CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204026Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 204026 SUPPL # HFD #

Trade Name Pomalyst

Generic Name Pomalidomide

Applicant Name Celgene Corporation

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Amy Baird
Title: Regulatory Project Manager
Date: January 15, 2013

Name of Office/Division Director signing form: Ann T. Farrell, M.D.
Title: Director, Division of Hematology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THERESA A CARIOTI
02/08/2013

ANN T FARRELL
02/08/2013

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 204026 | Supplement Number: _____ | NDA Supplement Type (e.g. SE5): _____

Division Name:DHOP | PDUFA Goal Date: 2/10/2013 | Stamp Date: 4/10/2012

Proprietary Name: Pomalyst

Established/Generic Name: Pomalidomide

Dosage Form: Capsules

Applicant/Sponsor: Celgene Corporation

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY C BAIRD
01/23/2013

DEBARMENT CERTIFICATION

Celgene Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Graham Burton, MD
Senior Vice President, Regulatory Affairs
Pharmacovigilance & Compliance

27th January 2012
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 204026 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: **Pomalyst** Established/Proper Name: **pomalidomide** Dosage Form: **capsules**		Applicant: **Celgene Corporation** Agent for Applicant (if applicable):
RPM: Amy Baird		Division: Division of Hematology Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY **action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.**

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
◎ Proposed action ◎ User Fee Goal Date is 2/10/2013	☒ AP ☐ TA ☐ CR
◎ Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf).	☒ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): NME

☒ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☒ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☒ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
◦ Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
◦ Press Office notified of action (by OEP)	☒ Yes ☐ No
◦ Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other – ASCO Burst

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
◉ Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
◉ NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
◉ (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
◉ (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
◉ (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
◉ NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
◉ Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
◉ Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
◉ [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
◉ [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval 2/8/2013
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
◦ Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	1/30/2013
◦ Original applicant-proposed labeling	4/10/2012
◦ Example of class labeling, if applicable	Revlimid, Thalomid

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
◦ Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	1/30/2013
◦ Original applicant-proposed labeling	4/10/2012
◦ Example of class labeling, if applicable	Revlimid, Thalomid
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
◦ Most-recent draft labeling	1/14/2013
❖ Proprietary Name ◦ Acceptability/non-acceptability letter(s) *(indicate date(s))* ◦ Review(s) *(indicate date(s)* ◦ *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Acceptable letter 12/7/2012 Proprietary name review (acceptable) 12/7/2012 Unacceptable letter 7/6/2012 Proprietary name review (unacceptable) 7/6/2012
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 1/16/2013 ☒ DMEPA 12/7/2012; 8/27/2012 ☒ DMPP/PLT (DRISK) 12/21/2012 ☒ ODPD (DDMAC) 1/9/2013; 12/14/2012; ☐ SEALD ☐ CSS ☐ Other reviews ,
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	RPM Filing Review 1/15/2013
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
◦ Applicant is on the AIP	☐ Yes ☒ No

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

◦ This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* ◦ Date reviewed by PeRC N/A If PeRC review not necessary, explain: Orphan Designation Granted 1/15/2003 for Multiple Myeloma ◦ Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	Pediatric page not reviewed by PeRC b/c orphan status. Pediatric Page to be entered into DARRTS as memo to file once approval action taken. ☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	1/24/2013 (2); 1/23/2013; 1/22/2013; 1/9/2013 (3); 12/21/2012; 12/19/2012; 12/18/2012; 12/7/2012; 11/30/2012; 11/21/2012; 11/9/2012; 11/5/2012; 10/31/2012; 10/18/2012; 10/5/2012; 9/12/2012; 8/31/2012 (2); 8/27/2012; 6/15/2012; 6/6/2012; 5/14/2012;
❖ Internal memoranda, telecons, etc.	12/10/2012; 8/3/2012; 5/25/2012; 5/3/2012
Minutes of Meetings	
◦ Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
◦ If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
◦ Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 9/13/2011
◦ EOP2 meeting *(indicate date of mtg)*	☐ No mtg 2/15/2011
◦ Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
◦ Date(s) of Meeting(s)	
◦ 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 2/7/2013
Division Director Summary Review *(indicate date for each review)*	☐ None 2/7/2013
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 12/21/2012
PMR/PMC Development Templates *(indicate total number)*	☐ None 9 PMRs and 1 PMC
Clinical Information[6]	
❖ Clinical Reviews	
◦ Clinical Team Leader Review(s) *(indicate date for each review)*	12/20/2012 Co-signed primary review

[6] Filing reviews should be filed with the discipline reviews.

◦ Clinical review(s) *(indicate date for each review)*	Review 12/20/2012 Filing Review 6/6/2012
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See 12/20/2012 Clinical Review (pages 18-19)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	12/7/2012; 4/10/2012 ☐ None 2/7/2013; 2/4/2013; 1/25/2013; 1/22/2013; 1/4/2013; 10/5/2012
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested Review 9/27/2012 OSI Letters 9/20/2012; 10/10/2012
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None 12/17/2012 Co-signed primary review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 12/17/2012 Co-signed primary review
Statistical Review(s) *(indicate date for each review)*	☐ None Review 12/17/2012 Filing Review 6/13/2012
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 12/20/2012 Co-signed primary review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Review 12/20/2012 Filing Review 6/20/2012
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
◦ ADP/T Review(s) *(indicate date for each review)*	☐ None 12/13/2012
◦ Supervisory Review(s) *(indicate date for each review)*	☐ None 12/13/2012
◦ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None Review 12/12/2012 Filing Review 5/29/2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
◦ ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
◦ Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None Co-signed primary review 1/15/2013, 12/14/2012
◦ Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None Product Quality Reviews 1/15/2013; 12/14/2012; Filing Review 6/11/2012 ONDQA Biopharm Review 12/14/2012 Filing Review 6/7/2012
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed Review 9/6/2012 Filing Review 6/22/2012
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See 12/14/2012 CMC Review (page 135)
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 1/24/2013 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Baird, Amy

From: Baird, Amy
Sent: Tuesday, January 22, 2013 2:48 PM
To: Christina Kish; Paul McInulty
Subject: NDA 204026 Pomalyst - REMS Assessment Report

Christina and Paul,

Below is a proposal for the items that should be included in each REMS Assessment report for Pomalidomide. Please let me know if Celgene agrees. Also, this assessment plan should be included in the REMS supporting document.

Each Assessment report must provide an evaluation of the following:

1. Pregnancies
   a. Number of pregnancies reported during the assessment reporting period and annually for each reporting period
   b. Outcome of each pregnancy
   c. Follow-up of outstanding pregnancy reports from previous assessment reporting period
   d. Root cause analysis of each reported pregnancy
   e. Link to most recent PSUR report on pregnancies worldwide; discussion of any new information provided in the PSUR regarding pregnancy

(b) (4)

2. Reporting on the restricted distribution program:
   a. Registered pharmacies, physicians, and patients during the current reporting period and during each previous annual reporting period: new and ongoing

   b. Patient demographics: for current reporting period and for previous reporting periods: gender, age diagnosis, females of reproductive potential (FRP)

(b) (4)

   d. Number of female patients for whom pregnancy testing can be discontinued because menopause has been documented by FSH/LH levels

3. Documentation of safe use conditions (via "mandatory survey")
   a. Listing of flags identified, reasons, and actions taken to correct: Provide by month for the reporting period; and summarize findings from each previous assessment report
   b. Flagged prescriptions/documentations of safe use of particular interest include those that have the potential of allowing a pregnant patient access to the drug and those that result in a delay or interruption of treatment:
      i. Number and proportion of flagged prescriptions intended for a patient who is a female of reproductive potential due to lack of documentation of negative pregnancy test; positive pregnancy test; delay in obtaining pregnancy test;
      ii. Number and proportion of flags that caused a delay in treatment initiation or a gap in therapy for the patient; provide the time to resolution of flags (mean, minimum, maximum) and include a graph of time to resolution vs. numbers of prescriptions (or number of mandatory surveys

conducted to document safe use conditions) for the reporting period and for each previous reporting period

4. An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals such elements should be modified.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2122
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
01/22/2013

Baird, Amy

From: Baird, Amy
Sent: Wednesday, January 09, 2013 4:21 PM
To: Christina Kish; 'Paul McInulty'
Subject: NDA 204026 Pomalidomide - FDA Proposed Labeling

Attachments: Labeling 11-6-2012 v5.doc

Christina and Paul,

Please refer to the NDA application for NDA 204026 Pomalidomide dated April 10, 2012, which provides for the proposed indication "Pomalidomide in combination with dexamethasone is indicated for patients with relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy."

We also refer to the revised Pomalyst labeling submitted on January 4, 2013. The following items were identified as requiring revision:

1. In your latest label revision, Table 4, serious adverse events was deleted from page 10 and 11, without explanation. The mentioned table should be placed back into the label.
2. Your rationale for not including neuropathy, confusional state and dizziness, in the Warning and Precaution section of the label are not acceptable. Physicians should be informed about these adverse events in making treatment decisions. Therefore, the adverse events of neuropathy, dizziness and confusional state should be included in the Warnings and Precautions section of the label.
3. You should add non-promotional language in the in the Warnings and Precautions section of the label describing the incidence of AML in patients treated with pomalidomide. In addition you should provide the denominator of the 19 cases of AML that you identified in the data search.

The latest proposed labeling from the FDA is attached. Please use this version of the labeling when responding to the comments above. You will notice the labeling has been updated to include edits to the Medication Guide and the package insert contains edits from the Maternal Health review team. This is not the final proposed FDA labeling and additional edits are forthcoming.

Also, please accept the FDA edits you agree with. Please provide a revised label NLT Thursday, January 10, 2013, 3:00pm EST (via email).

Labeling 11-6-2012 v5.doc (626...

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2122
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
01/09/2013

Baird, Amy

From: Baird, Amy
Sent: Wednesday, January 09, 2013 1:12 PM
To: Christina Kish; 'Paul McInulty'
Subject: NDA 204026 Pomalidomide REMS - FDA Comments

Attachments: January 4 2013 FDA markup for review rems.doc; Combined Pomalyst REMS materials.pdf

Christina and Paul,

Please refer to the Risk Evaluation and Mitigation Strategy (REMS) proposal for Pomalidomide.

We have reviewed documents and have the following comments for you, please see the attached documents below.


January 4 2013 FDA markup for...


Combined Pomalyst REMS materia...

Please submit the revised REMS by next Monday, January 14, 2013.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2122
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
01/09/2013

Baird, Amy

From: Baird, Amy
Sent: Wednesday, January 09, 2013 11:20 AM
To: Christina Kish; 'Paul McInulty'
Subject: NDA 204026 Pomalidomide - FDA DMEPA Comments

Christina and Paul,

Please refer to the NDA application for NDA 204026 Pomalidomide dated April 10, 2012, which provides for the proposed indication "Pomalidomide in combination with dexamethasone is indicated for patients with relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy."

The FDA Office of Medication Error Prevention and Risk Management has completed their review of the proposed container labels and package insert for areas of vulnerability and medication errors. Please provide a response to the following comments NLT Monday, January 14, 2013, 10:00am.

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Labels 1 mg, 2 mg, 3 mg, and 4 mg

1. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10(g)(2).

2. Delete or minimize the graphic that appears to the left of the proprietary name as this graphic competes for the end user's attention with the proprietary name.

3. Ensure the proprietary name on the container label is presented in title case (i.e. Pomalyst) to ensure the readability of the proprietary name.

B. Insert Labeling

a. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear in the Highlights of Prescribing and Dosage and Administration sections of package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations in the body of the text as follows:

- Revise the "/" symbol appearing throughout the Dosage and Administration section to read "per".
- Revise the '≤' and '≥'symbols appearing in the body of the text of sections 2.1 (Dose Modifications), to read "less than or equal to" and "more than or equal to" respectively.
- Information regarding product administration should be appear together. As such, revise the statement (b) (4)

The comments regarding the package insert can be fixed after we send the FDA proposed labeling again. However, comments regarding the container labels should be addressed and submitted by Monday, January 14, 2013, 10:00am.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2122
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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AMY C BAIRD
01/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204026

LABELING PMR/PMC DISCUSSION COMMENTS

Celgene Corporation
Attention: Paul McInulty
Director, Regulatory Affairs
400 Connell Drive, Suite 7000
Berkeley Heights, NJ 07922

Dear Mr. McInulty:

Please refer to your April 10, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pomalidomide Capsules.

We also refer to our June 15, 2012, letter in which we notified you of our target date of December 23, 2012, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On April 10, 2012, we received your April 10, 2012, proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. Several sections of the labeling are still under review and further comments are forthcoming. Please provide a response to the labeling by January 3, 2013. Also, please accept all edits to the labeling with which you agree.

If you have any questions, call me at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Amy Baird
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE: Labeling

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

AMY C BAIRD
12/21/2012

Baird, Amy

From: Baird, Amy
Sent: Wednesday, December 19, 2012 12:09 PM
To: 'Paul McInulty'; 'Christina Kish'
Subject: NDA 204026 Pomalidomide - FDA Request for PMR & PMCs

Christina and Paul,

Please refer to the NDA application for NDA 204026 Pomalidomide dated April 10, 2012, which provides for the proposed indication "Pomalidomide in combination with dexamethasone is indicated for patients with relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy."

As we continue our review of your NDA, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief summaries are intended to describe the main trial characteristics of interest. Please supplement and comment to clarify mutually acceptable descriptions of the key trial elements. We are available to discuss by tcon if needed.

Upon mutual agreement for the content and timing of all PMR/PMCs, submit to us, both by email and officially, the full text and the timeline for each PMR and PMC study/trial you will perform with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Milestone times only need a month and year. For milestone calculations purposes only, assume that an approval occurs on the PDUFA date.

Note that the "Final Protocol Submission" date is the date on (or before) which you submit a complete protocol that has already received full concurrence by FDA. We suggest that you consider realistic milestone times.

Final PMR designation numbers will be assigned later.

#1

NDA/BLA #	204026		
Product Name:	Pomalyst		
PMR/PMC Description:	PMR (Subpart H): Conduct a randomized controlled trial (MM-007) that isolates and demonstrates the efficacy and safety of pomalidomide in patients with previously treated multiple myeloma		
PMR/PMC Schedule Milestones:	Final Protocol Submission:	MM/YYYY	
	Study/Trial Completion:	MM/YYYY	
	Final Report Submission:	MM/YYYY	
	Other:	MM/YYYY	

Provide the protocol for FDA review and concurrence before initiating the trial.

#2

NDA/BLA #	204026	
Product Name:	Pomalyst	
PMR/PMC Description:	PMR (FDAAA Safety): Conduct a randomized controlled trial (MM-003) of the combination of pomalidomide and dexamethasone in patients with previously treated multiple myeloma	
PMR/PMC Schedule Milestones:	Final Protocol Submission:	MM/YYYY
	Study/Trial Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY
	Other:	MM/YYYY

Provide the protocol for FDA review and concurrence before initiating the trial.

#3

NDA/BLA # 204026
Product Name: Pomalyst

PMR/PMC Description: PMR (FDAAA Safety):
PMR (FDAAA Safety): Conduct an epidemiologic study to address the questions detailed below:
1. What is the failure rate for each of the different types of thromboembolic prophylaxis (e.g., antiplatelet or anticoagulant therapy) for multiple myeloma patients treated with a pomalidomide-containing regimen?
2. What is the failure rate for each type of Deep Vein Thrombosis (DVT) treatment (e.g., dose-adjusted heparin, low molecular weight heparin, coumadin, or other oral anticoagulants) for those patients with multiple myeloma and a DVT who continue to receive ongoing treatment with pomalidomide?
3. What is the failure rate for each type of post-DVT thromboembolic prophylaxis for those patients with multiple myeloma and a DVT who continue to receive ongoing treatment with pomalidomide?
This prospective epidemiologic study will enroll select patients identified in the (b) (4) program, and collect the necessary additional data on these patients to further evaluate occurrences of thrombosis and anticoagulant use.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	MM/YYYY
	Study/Trial Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY
	Other:	MM/YYYY

Provide the protocol for FDA review and concurrence before initiating the trial.

#4

NDA/BLA # 204026
Product Name: Pomalidomide

PMR/PMC Description: PMR (FDAAA Safety): Determine the effect of hepatic impairment in patients with baseline hepatic impairment receiving pomalidomide, since the drug is metabolized by the liver per FDA guidance.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	5/31/2013
	Study/Trial Completion:	5/31/2015
	Final Report Submission:	9/30/2015
	Other:	MM/DD/YYYY

Provide the protocol for FDA review and concurrence before initiating the trial.

#5

NDA/BLA # 204026
Product Name: Pomalidomide

PMR/PMC Description: PMR (FDAAA Safety): Renal impairment trial in patients with baseline renal impairment and those on chronic dialysis to determine the safety and PK in the renal impairment population, conducted per FDA guidance.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	2/17/2012
	Study/Trial Completion:	5/31/2015
	Final Report Submission:	9/30/2015
	Other:	MM/DD/YYYY

Provide the protocol for FDA review and concurrence before initiating the trial.

#6

NDA/BLA #	204026	
Product Name:	Pomalidomide	
PMR/PMC Description:	PMR (Subpart H): Determine the effect of CYP3A Induction, which may DECREASE drug exposure, on the PK of Pomalidomide.	
PMR/PMC Schedule Milestones:	Final Protocol Submission:	5/31/2013
	Study/Trial Completion:	5/31/2014
	Final Report Submission:	9/30/2014
	Other:	MM/DD/YYYY

Provide the protocol for FDA review and concurrence before initiating the trial.

#7

NDA/BLA #	204026	
Product Name:	Pomalidomide	
PMR/PMC Description:	PMR (FDAAA Safety): Determine the effect of CYP3A Inhibition, which may increase drug exposure and thereby drug toxicity, on pomalidomide PK	
PMR/PMC Schedule Milestones:	Final Protocol Submission:	5/31/2013
	Study/Trial Completion:	5/31/2014
	Final Report Submission:	9/30/2014
	Other:	MM/DD/YYYY

Provide the protocol for FDA review and concurrence before initiating the trial.

#8

NDA/BLA #	204026	
Product Name:	Pomalidomide	
PMR/PMC Description:	PMC: Determine the effects of smoking (CYP1A2 Inducer) on PK of pomalidomide.	
PMR/PMC Schedule Milestones:	Final Protocol Submission:	5/31/2013
	Study/Trial Completion:	5/31/2015
	Final Report Submission:	9/30/2015
	Other:	MM/DD/YYYY

Provide the protocol for FDA review and concurrence before initiating the trial.

#9

NDA/BLA #	204026	
Product Name:	Pomalidomide	
PMR/PMC Description:	PMR (FDAAA Safety Study): Determine the effect of food on absorption and PK of the drug in an appropriate population to enable description of food effect dosing information to be added to the label Effect Study	
PMR/PMC Schedule Milestones:	Final Protocol Submission:	2/28/2013
	Study/Trial Completion:	12/31/2013
	Final Report Submission:	2/28/2014
	Other:	MM/DD/YYYY

Provide the protocol for FDA review and concurrence before initiating the trial.

#10

NDA/BLA #	204026	
Product Name:	Pomalidomide	
PMR/PMC Description:	PMR (FDAAA Safety): Conduct a QT Prolongation trial per the FDA guidance to assess the effect of Pomalidomide on the QT interval.	
PMR/PMC Schedule Milestones:	Final Protocol Submission:	2/28/2013

Study/Trial Completion:	5/31/2014
Final Report Submission:	9/30/2014
Other:	MM/DD/YYYY

Provide the protocol for FDA review and concurrence before initiating the trial.

Please do not hesitate to contact me should you have any questions.

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2122
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
12/19/2012

Baird, Amy

From: Baird, Amy
Sent: Tuesday, December 18, 2012 2:54 PM
To: 'Paul McInulty'; 'Christina Kish'
Subject: NDA 204026 Pomalidomide - FDA Clinical Request

Please refer to the NDA application for NDA 204026 Pomalidomide dated April 10, 2012, which provides for the proposed indication "Pomalidomide in combination with dexamethasone is indicated for patients with relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy."

Per the request of the FDA clinical review team, please provide a report regarding the number of patients treated with pomalidomide who subsequently developed AML. Please include the safety narrative for each patient.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2122
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
12/18/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	December 10, 2012
TIME:	3:00PM (EST)
LOCATION:	TCON/CDER WO 2560
APPLICATION:	NDA 204026
DRUG NAME:	Pomalidomide
TYPE OF MEETING:	FDA initiated TCON
MEETING CHAIR:	Nallaperumal Chidambaram, Acting Branch Chief
MEETING RECORDER:	Jewell Martin, Regulatory Health Project Manager
MEETING PURPOSE:	To discuss outstanding issues before GRMP Deadline

FDA Attendees:
Nallaperumal Chidambaram, PhD, Acting Branch Chief, Branch II
William Adams, PhD, CMC Reviewer
Angelica Dorantes, Biopharmaceutics Team Lead
Tien-Mien Chen, PhD, Biopharmaceutics Reviewer
Jewell Martin, MA, MBA, PMP, Regulatory Project Manager, ONDQA

Celgene Attendees
Rick Couch, Executive Director, Regulatory CMC
Sigita Zibas, PhD, Associate Director, Regulatory CMC
Paul Kurtulik, PhD, VP, Quality and Development
Anthony Tutino, MS, RPh, Executive Director, Pharmaceutical Development
Anil Menon, Director, Pharmaceutical Development
Paul McInulty, Director, Regulatory Affairs

Meeting Background:
The Agency requested a teleconference with the sponsor on December 6, 2012, to discuss outstanding issues. On December 7, 2012, the Agency emailed discussion points to the sponsor in preparation for the TCON on December 10, 2012. In an email sent on December 10, 2012, the sponsor stated that they are "in agreement with points drug substance and drug product points 1-8, but would like to discuss the drug substance retest period (point 4), provide an update and discuss the bulk hold time (point 6), and discuss the drug product shelf life (point 7)." Agency questions and discussion points are listed below.

Biopharmceutics

1. The proposed dissolution acceptance criterion of Q(b) (4)% at 45 min is not supported by the provided dissolution data. Therefore, the dissolution acceptance criterion should be tightened to Q=(b) (4)% at 45 min. Nevertheless, it must be recognized that some batches may require Stage 2 and, occasionally, Stage 3 testing. Please provide the updated specification table for the drug product with the revised dissolution criterion.

Discussion: None

Action: Sponsor agreed to the change and will provide revised NDA sections. The response will be submitted as Email courtesy copy by Wednesday, December 12, 2012 with formal submission as soon as available.

2. We have concerns that the observed variations in [redacted] (b) (4) among the batches could be due to the [redacted] (b) (4) in the drug product. Please analyze the relationship between the [redacted] (b) (4) and the [redacted] (b) (4) in the drug product and provide the information.

Discussion: None

Action: Sponsor agreed to submit the requested data and analysis by Friday, December 14, 2012.

Drug Substance

1. Your response 4 from the 26 Nov 2012 amendment referenced enantiomeric content by Chiral HPLC test results obtained at ICH LT/ [redacted] (b) (4) for lot CMLW174/06-002, however this data was not provided in the application. Provide available test data on enantiomeric content from any of the submitted stability studies.

Discussion: None

Action: Sponsor agreed to submit the data by Wednesday, December 12, 2012.

2. Your response 5b from the 26 Nov 2012 amendment did not include the calculation of reported values for the [redacted] (b) (4) Please provide this information.

Discussion: None

Action: Sponsor agreed to submit the requested data by Wednesday, December 12, 2012.

3. We disagree with your proposal to report "assay, as is" since this would introduce variability and obscure trend analysis of product release and stability data. We recommend reporting [redacted] (b) (4) assay values.

Discussion: None

Action: Sponsor agreed to the requested change. Revised NDA sections will be submitted by Wednesday, December 12, 2012.

4. Please note that the (b) (4) lots contain unknown impurities which does not appear in drug substance from (b) (4). In addition, there is no clinical experience with drug substance from (b) (4). Retest period should be based on primary stability data. The stability study data on (b) (4) lots was obtained using an earlier analytical method, therefore these studies are being considered as supportive, instead of primary stability data.

   Based on our evaluation of the available room temperature stability data, we have the following recommendations:

   - the primary (b) (4) data supports an initial retest period of (b) (4)
   - the primary (b) (4) data supports an initial retest period of (b) (4)
   - the supportive (b) (4) data supports an initial retest period of (b) (4)
   - the supportive (b) (4) data supports an initial retest period of (b) (4)

   Based on the above, we recommend that you propose a retest period. If desirable, we will be willing to discuss this matter to establish an appropriate initial retest period.

Discussion: The Sponsor stated that they are prepared to submit additional long term stability data to (b) (4) on both manufacturing sites to support the proposed initial retest period. The Agency noted that this would constitute a major amendment and extend the review clock. The Sponsor did not want to extend the review clock.

During the discussion, it was also noted that (b) (4) material was used in 3 clinical trials (studies MMM001, MM03 and MM010), thus there is safety data to address the differences in impurity profiles for materials from the two manufacturing sites. This supports the pooling of stability study data. It was agreed that if the cited clinical trials were found to used (b) (4) drug substance, then pooled data would support an initial retest period of (b) (4) with storage at (b) (4)

Action: The Sponsor agreed to provide the clinical trial information and to revise the appropriate NDA sections to reflect an initial retest period of (b) (4) with storage at (b) (4) This information is to be submitted by Wednesday, December 12, 2012.

5. We find your proposal for reduced testing (b) (4) in the post-approval stability protocol not acceptable. Revise this protocol to include testing at 3,6,9,18 months.

Discussion: None

Action: Sponsor agreed to the requested change. Revised NDA sections will be submitted by Wednesday, December 12, 2012.

Drug Product

6. In the absence of stability information on bulk capsules in the proposed shipping/storage container or the effect of bulk storage/shipment on the stability of capsules in their commercial packaging systems, your proposal for holding

bulk capsules for (b) (4) is not acceptable. Reduce the maximum storage time to (b) (4) until data supporting an extension is submitted to the application.

Discussion: The sponsor stated that they have an on-going stability study on capsules in their bulk container and that ICH LT (b) (4) data is available. It was agreed that an initial (b) (4) maximum hold time for bulk capsules would be accepted if this data showed acceptable stability.

Action: The Sponsor agreed to revise the NDA to reflect an initial maximum hold time of (b) (4) and to submit the study data by Monday, December 17, 2012.

7. Please note that stability studies for capsules made at Celgene Sarl using drug substance from (b) (4) consistently report an unknown impurity and there is no clinical experience for capsules made with drug substance from (b) (4) In addition, batch release data for capsules made at Celgene Sarl using drug substance from (b) (4) report an impurity at (b) (4) Stability studies for capsules made at (b) (4) with drug substance from (b) (4) report total impurities at (b) (4). Based on this your expiry dating period should be based on primary stability data and demonstrated comparability with the drug product manufactured at other intended site for commercial manufacture.

   The following list provides the amount of data submitted from different manufacturing sites:

   - (b) (4); 1mg/2mg- supportive studies to (b) (4)
   - (b) (4); 3mg/4mg - supportive studies to (b) (4)
   - (b) (4); 1mg/2mg – primary studies to (b) (4)
   - (b) (4); 3mg/4mg – primary studies to (b) (4)
   - (b) (4); 1mg/2mg – no data
   - (b) (4); 3mg/4mg – no data
   - (b) (4); 1mg/2mg – no data
   - (b) (4); 3mg/4mg – no data
   - (b) (4); 1mg/2mg – primary studies to (b) (4)
   - (b) (4); 3mg/4mg – primary studies to (b) (4)

   Based on the above, we recommend that you propose a shelf-life supported by data. If desirable, we will be willing to discuss this matter to establish an appropriate expiry dating period.

Discussion: The Sponsor proposes to use drug substance from both suppliers interchangeably and does not feel it is necessary to designate site specific suppliers. The Agency stated that if the sponsor can successfully address the unknown impurity, then stability data can be pooled. It was noted that the impurity was not a safety issue (due its consistent low level) rather it is a quality issue due to inconsistency of the impurity profiles.

The Sponsor stated that they have investigated the appearance of impurity (b) (4) and found it to be a laboratory anomaly. They agreed to provide copies of HPLC

chromatograms for blank, assay and reference standards, all showing the presence of the peak, to support this conclusion.

After further discussion and provided the above information is aceptable, the Agency agreed to accept a proposed initial expiry period of 18M with storage at USP CRT for capsules made with drug substance from either manufacturing site.

Action: The Sponsor agreed to provide the HPLC information and revise the appropriate NDA sections. This information is to be submitted by December 12, 2012.

8. We find that your proposal for reduced testing (b) (4) in the post-approval stability protocol is not acceptable. Revise this protocol to include testing at 3,6,9,18 months.

Discussion: None

Action: Sponsor agreed to the requested change. Revised NDA sections will be submitted by Wednesday, December 12, 2012.

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/s/

JEWELL D MARTIN
01/16/2013

NALLAPERUM CHIDAMBARAM
01/23/2013

From: Martin, Jewell
To: "Sigita Zibas"
Subject: NDA 204026 TCON Discussion Points for December 10, 2012
Date: Friday, December 07, 2012 4:01:00 PM

Hello Dr. Zibas,

Per our discussion please find points for discussion at our TCON scheduled for Monday, December 10, 2012, 3:00PM (EST). Please provide a conference line number for our meeting and feel free to contact me if you have any questions.

Drug Substance

1. Your response 4 from the 26 Nov 2012 amendment referenced enantiomeric content by Chiral HPLC test results obtained at ICH LT/ (b) (4) for lot CMLW174/06-002, however this data was not provided in the application. Provide available test data on enantiomeric content from any of the submitted stability studies.

2. Your response 5b from the 26 Nov 2012 amendment did not include the calculation of reported values for the (b) (4). Please provide this information.

3. We disagree with your proposal to report "assay, as is" since this would introduce variability and obscure trend analysis of product release and stability data. We recommend reporting (b) (4) assay values.

4. Please note that the (b) (4) lots contain unknown impurities which does not appear in drug substance from (b) (4). In addition, there is no clinical experience with drug substance from (b) (4). Retest period should be based on primary stability data. The stability study data on (b) (4) lots was obtained using an earlier analytical method, therefore these studies are being considered as supportive, instead of primary stability data.

   Based on our evaluation of the available room temperature stability data, we have the following recommendations:
   - the primary (b) (4) data supports an initial retest period of (b) (4)
   - the primary (b) (4) data supports an initial retest period of (b) (4)
   - the supportive (b) (4) data supports an initial retest period of (b) (4)
   - the supportive (b) (4) data supports an initial retest period of (b) (4)

   Based on the above, we recommend that you propose a retest period. If desirable, we will be willing to discuss this matter to establish an appropriate initial retest period.

5. We find your proposal for reduced testing (annual only) in the post-approval stability protocol not acceptable. Revise this protocol to include testing at 3,6,9,18 months .

Drug Product

6. In the absence of stability information on bulk capsules in the proposed shipping/storage container or the effect of bulk storage/shipment on the stability of capsules in their commercial packaging systems, your proposal for holding bulk capsules for (b) (4) is not acceptable. Either reduce the maximum storage time to (b) (4) until data supporting an extension is submitted to the application.

7. Please note that stability studies for capsules made at Celgene Sarl using drug substance from (b) (4) consistently report an unknown impurity and there is no clinical experience for capsules made with drug substance from (b) (4) In addition, batch release data for capsules made at Celgene Sarl using drug substance from (b) (4) report an impurity at (b) (4) Stability studies for capsules made at (b) (4) with drug substance from (b) (4) report total impurities at (b) (4) Based on this your expiry dating period should be based on primary stability data and demonstrated comparability with the drug product manufactured at other intended site for commercial manufacture.

The following list provides the amount of data submitted from different manufacturing sites:

- (b) (4); 1mg/2mg- supportive studies to (b) (4)
- (b) (4); 3mg/4mg - supportive studies to (b) (4)
- (b) (4); 1mg/2mg – primary studies to (b) (4)
- (b) (4); 3mg/4mg – primary studies to (b) (4)
- (b) (4); 1mg/2mg – no data
- (b) (4); 3mg/4mg – no data
- (b) (4); 1mg/2mg – no data
- (b) (4); 3mg/4mg – no data
- (b) (4); 1mg/2mg – primary studies to (b) (4)
- (b) (4); 3mg/4mg – primary studies to (b) (4)

Based on the above, we recommend that you propose a shelf-life supported by data. If desirable, we will be willing to discuss this matter to establish an appropriate expiry dating period.

8. We find your proposal for reduced testing (b) (4) in the post-approval stability protocol not acceptable. Revise this protocol to include testing at 3,6,9,18 months

Biopharmceutics

1. The proposed dissolution acceptance criterion of Q (b) (4) % at 45 min is not supported by the provided dissolution data. Therefore, the dissolution acceptance criterion should be tightened to Q= (b) (4) % at 45 min. Nevertheless, it must be recognized that some batches may require Stage 2 and, occasionally, Stage 3 testing. Please provide the updated specification table for the drug product with the revised dissolution criterion.

2. We have concerns that the observed variations in % dissolution of pamolidomide among the batches could be due to the [redacted] (b) (4). Please analyze the relationship between the % dissolution of pamolidomide and the [redacted] (b) (4) in the drug product and provide the information.

Please confirm receipt this email.

Best,
Jewell

Jewell D. Martin, MA, MBA, PMP
Product Quality Regulatory Project Manager
Office of New Drug Quality Assessment
Food and Drug Administration
White Oak Building 21, Rm 2625
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(301) 796-2072
jewell.martin@fda.hhs.gov

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/s/

JEWELL D MARTIN
12/18/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204026

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Celgene Corporation
400 Connell Drive, Suite 7000
Berkeley Heights, NJ 07922

ATTENTION: Paul McInulty
Director, Regulatory Affairs

Dear Mr. McInulty:

Please refer to your New Drug Application (NDA) dated April 10, 2012, received April 10, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Pomalidomide Capsules, 1 mg, 2 mg, 3 mg, and 4 mg.

We also refer to your September 19, 2012, correspondence, received September 19, 2012, requesting review of your proposed proprietary name, Pomalyst. We have completed our review of the proposed proprietary name, Pomalyst and have concluded that it is acceptable.

The proprietary name will be re-reviewed 90 days prior to approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. Additionally, if **any** of the proposed product characteristics as stated in your September 19, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

(See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cristina Makela, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-6632. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Amy Baird at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
12/07/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204026

INFORMATION REQUEST

Celgene Corporation
Attention: Sigita Zibas, PhD
Director ,Global Regulatory CMC
400 Connell Drive, Suite 7000
Berkeley Heights, NJ 07922

Dear Dr. Zibas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pomalidomide (Capsules).

We also refer to your submission dated October 29, 2012, received on October 31, 2012.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by December 3, 2012, in order to continue our evaluation of your NDA.

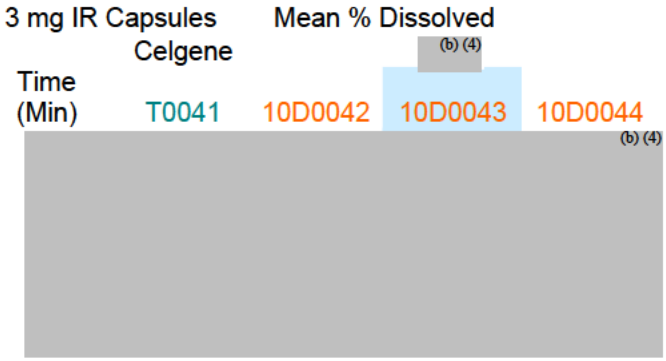
1. Please clarify if the capsule batches made at Celgene, Sarl site had been tested clinically. If not, a biowaiver request is needed in order to link it to the other proposed site, (b) (4) Also please submit the following for review, 1). A biowaiver request with your justification, and 2). Comparative dissolution profile data (*multipoint comparative dissolution mean profile data; mean and individual, n=12 capsules/batch*) and similarity (f2) values to support the waiver.

2. The mean dissolution data showed a trend that the tablets manufactured at Celgene, Sarl site had (b) (4) (Section 4 under Module 3.2.P.5 Control of Drug Product) than those tablets manufactured at (b) (4) site (Section 4 under Module 3.2.P.5 Control of Drug Product). Please provide your rationale/justification for the observed differences. Also, please provide a rationale as to why one of the three batches of each strength made at (b) (4) had (b) (4) (e.g., see tables below).

2 mg IR Capsules Mean % Dissolved

Celgene (b) (4)

Time (Min)	T0039	T0040	10D0039	10D0040	10D0041
(b) (4)					



If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Nallaperumal Chidambaram, PhD
Acting Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

NALLAPERUM CHIDAMBARAM
11/21/2012

Baird, Amy

From: Baird, Amy
Sent: Friday, November 30, 2012 11:43 AM
To: 'Marion Ceruzzi'; 'Paul McInulty'; 'Christina Kish'
Subject: NDAs 021880/S-029 Revlimid, 020785/S-048 Thalomid, 204026 Pomalidomide - Request for Word Version of REMS

Marion, Christina, and Paul,

Please refer to submissions dated November 26, 2012, to NDAs 021880/S-029 Revlimid and 020785/S-048 Thalomid. These submissions provided a newly proposed REMS based upon FDA feedback; however, the submissions only provide a .PDF version. Can you please submit to the Electronic Document Room a Word version of the REMS documents for both Revlimid and Thalomid?

Christina and Paul, when you submit the revised REMS for Pomalidomide, please also include a Word version.

Thanks,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2122
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
11/30/2012

Baird, Amy

From: Baird, Amy
Sent: Monday, November 05, 2012 4:10 PM
To: 'Paul McInulty'
Cc: Christina Kish
Subject: RE: NDA 204026 Pomalidomide - FDA Request re Labeling

Paul,

Thank you for your email below. The email was discussed amongst the FDA review team and we have the following response.

No. We recommend that you use the original data cut-off for your revised label. The clinical review team performed the safety analyses using the original data cut-off. We also recommend a 5% cut-off for Grade 3-4 TEAEs.

However, your proposal to make other minor revisions is acceptable provided you mark them in track change format.

Please do not hesitate to contact me should you have any questions.

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2122
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

From: Paul McInulty [mailto:PMcInulty@celgene.com]
Sent: Monday, November 05, 2012 2:39 PM
To: Baird, Amy
Cc: Christina Kish
Subject: RE: NDA 204026 Pomalidomide - FDA Request re Labeling

Dear Amy

I hope that you are well. I have now been able to discuss the request with the team who are currently re-running the safety tables to enable us to update the USPI and provide the FDA.

Within the updated version of the USPI, we also like to:

- Update the safety data with that from the Day 120 update.
- Use a (b) (4) cut-off for Grade 3/4 TEAE's.
- Make a few other minor revisions to related text that we believe can improve the clarity of - we will

mark these in track-changes

I will be in a position to provide the updated USPI to you on Wednesday 5th November 2012.

Is this acceptable to the agency?

Thank-you and kind regards

Paul

From: Baird, Amy [mailto:Amy.Baird@fda.hhs.gov]
Sent: 01 November 2012 17:48
To: Paul McInulty
Cc: Christina Kish
Subject: RE: NDA 204026 Pomalidomide - FDA Request re Labeling

Okay..thank you for the update. I'll let the team know that you may be late with the response.

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2122
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

From: Paul McInulty [mailto:PMcInulty@celgene.com]
Sent: Thursday, November 01, 2012 1:11 PM
To: Baird, Amy
Cc: Christina Kish
Subject: RE: NDA 204026 Pomalidomide - FDA Request re Labeling

Dear Amy

Thank-you for your email, and I acknowledge receipt of it.

I will discuss with the team and we will try to provide a response by your deadline, however please be informed that currently all of our New Jersey sites lack power as do most of the team members.

However, we will do our best.

Kind regards

Paul

From: Baird, Amy [mailto:Amy.Baird@fda.hhs.gov]
Sent: 31 October 2012 15:33
To: Christina Kish; Paul McInulty
Subject: NDA 204026 Pomalidomide - FDA Request re Labeling

Christina and Paul,

Please refer to the NDA application for NDA 204026 Pomalidomide dated April 10, 2012, which provides for the proposed indication "Pomalidomide in combination with dexamethasone is indicated for patients with relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy."
Per the request of the FDA review team, provide a response to the following labeling comments. Please provide your response via electronic submission NLT November 5, 2012.

ise Section 6 of your proposed label to include the following changes:

nclude all treatment-emergent adverse events, regardless of attribution of relatedness to pomalidomide.

Jse American spelling for the terms.

or Table 2, you can use a cut-off of (b) (4) of patients. The cut-offs for Tables 3 and 4 (5% and 2 patients, respectively) are acceptable.

Revise Tables 2, 3, and 4 to the following structure:

(b) (4)

(b) (4)

(b) (4)

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2122
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
11/05/2012

Baird, Amy

From: Baird, Amy
Sent: Wednesday, October 31, 2012 11:33 AM
To: Christina Kish; 'Paul McInulty'
Subject: NDA 204026 Pomalidomide - FDA Request re Labeling

Christina and Paul,

Please refer to the NDA application for NDA 204026 Pomalidomide dated April 10, 2012, which provides for the proposed indication "Pomalidomide in combination with dexamethasone is indicated for patients with relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy."

Per the request of the FDA review team, provide a response to the following labeling comments. Please provide your response via electronic submission NLT November 5, 2012.

Revise Section 6 of your proposed label to include the following changes:

1. Include all treatment-emergent adverse events, regardless of attribution of relatedness to pomalidomide.
2. Use American spelling for the terms.
3. For Table 2, you can use a cut-off of (b) (4) of patients. The cut-offs for Tables 3 and 4 (5% and 2 patients, respectively) are acceptable.
4. Revise Tables 2, 3, and 4 to the following structure:

(b) (4)

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2122
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
10/31/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDAs 20785, 21880, 204026

GENERAL ADVICE

Celgene Corporation
Attention: Marion Ceruzzi, PhD
Director of Regulatory Affairs
400 Connell Drive
Building 400, Office 4-7032
Berkeley Heights, NJ 07922

Dear Dr. Ceruzzi:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Revlimid (lenalidomide), Thalomid (thalidomide), and pomalidomide capsules.

We also refer to your December 29, 2011, submissions, containing a Risk Evaluation and Mitigation Strategy (REMS) modification proposal to harmonize the REMS programs for Thalomid and Revlimid. We have reviewed the referenced material and have the following comments/recommendations to facilitate your completion of the harmonization:

1. We agree with your overall approach for harmonizing the Revlimid and Thalomid REMS, and incorporating the pomalidomide REMS into the harmonized system, should pomalidomide be approved. We disagree with (b) (4)

2. We have made comments on the content of your REMS materials. However, we cannot comment to the ease of usability of the materials until we see the actual layout and formatting of the materials. Submit all program materials showing the actual design. Our specific comments on your December 29, 2011 submission are detailed below.

REMS Processes, Elements, and Educational Materials

- The REMS materials reference the websites www.revlimid.com and www.thalomid.com. Replace these references with the address of the new harmonized web portal. Also clarify if the product web addresses will direct users to the new harmonized web portal.

- We agree with the following
  - the Medication Guides can be removed from the REMS.
  - including an option for patients to return unused product to their HCP participants in the REMS; that is, the patients could return product to their Revlimid/Thalomid prescriber, or to the pharmacy that dispensed the Revlimid/Thalomid to them, in

addition to returning product directly to Celgene. Patients should not return product to HCPs who do not participate in the REMS.
  - your proposals for the timing of pregnancy testing and use of contraceptives within the REMS.
  - your revisions to the patient prescription form to remove unnecessary items, and to make editorial improvements.
  - your proposal to harmonize the period of validity of the prescription authorization numbers between the programs, and to lengthen the period of validity for females not of reproductive potential and men to 30 days.
  - maintaining the current pregnancy risk categories.

- We do not agree with (b) (4) At the September 27, 2011 meeting with you, the only items that the Agency agreed could be placed into the REMS Supporting Document (b) (4) are the dashboards for prescribers and pharmacists.

  The patient prescription form and all REMS educational materials, including the newly consolidated patient, pharmacist, and prescriber pieces, should be included as part of the REMS and should therefore be appended to the REMS. Any newly developed REMS materials, for example, the REMS items you listed in your September 24, 2012 email to the Agency, should be included in the REMS, appended to the REMS, and submitted to the Agency for review as part of a REMS modification.

- We agree that it is preferable to use numbers other than the DEA number for prescribers and the Social Security Number for patients as identification numbers within the REMS. (b) (4) We propose that, (b) (4), that the prescribers use their National Provider Identifier (NPI) number. This would lessen prescriber burden by using a number that the prescribers already know, (b) (4)

- **Prescriber Materials**
  - Instructions for Prescribers
    Information on the registration process for prescribers needs to be included in this document. General details on filling out the registration form and options for sending to the sponsor should be included.
    See Instructions for Prescribers (attached) for suggested track changes.

  - RevAssist. at a Glance
    See RevAssist at a Glance (attached) for suggested track changes.

  - Prescriber Registration Form
    See Prescriber Registration Form (attached) for suggested track changes.

  - Patient-Physician Agreement Forms
    See attached forms for suggested track changes.

- Prescriber Dashboard:
  Submit all web screen shots for Prescriber Dashboard for FDA comment.

- RevAssist Kit Housing Unit
  See RevAssist Kit Housing Unit (attached) for suggested track changes.

- **Pharmacists**
  - Instructions for Pharmacists and Pharmacist Quick Guide
    These two documents have repetitive information that should be combined into a simple communications piece. See revised Pharmacist Guide (attached) with suggested track changes.

  - Pharmacist Registration Form
    See Pharmacist Registration Form (attached) for suggested track changes.

  - Education and Counseling Checklist for Pharmacies (part of RevAssist only)
    See Education and Counseling Checklist (attached) for suggested track changes.

  - Pharmacist Web Portal Screen Shots:
    Submit all web screen shots for Pharmacist Web Portal for FDA comment.

- **Patients**
  - Patient Brochure
    See Patient Brochure (attached) with suggested track changes

Surveys

- We agree that the newly requested (in the 2010 REMS approval letters) prescriber and patient surveys of knowledge will not be needed to assess the REMS. We accept your counter proposal regarding these surveys.

- The "mandatory" surveys currently in the REMS must be maintained.

- We acknowledge your proposal to discontinue the "voluntary" surveys currently conducted within the REMS. To help us consider this proposal, we request the following information regarding the "voluntary" surveys. Please provide the following information about the "voluntary surveys" conducted since the REMS for Thalomid and Revlimid were approved in 2010. For each drug, please supply the following information.

  - Total patients who have enrolled in the REMS
  - The total number of patients who initially indicated they were willing to participate in the voluntary surveys (total, and by pregnancy risk category)
  - The number (and %) who responded to the voluntary surveys (total, and by pregnancy risk category, and by whether the participation was in the initial survey or the follow-up survey)
  - The number (and %) of wrong answers; the items answered incorrectly

- The number and items of wrong/concerning answers referred to Celgene for follow up with individual patients; the pregnancy category of the patients Celgene intervened with after wrong/concerning responses on the voluntary surveys
- The outcome of each intervention

General Comments

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Thalomid and Revlimid with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document, and the REMS Supporting Document be in a second MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in a single MS Word document.

Certification of accurate translation of REMS materials: Submit a statement to the NDAs that certifies that the Risk Evaluation and Mitigation Strategy (REMS) and all REMS materials translated to foreign-language(s) are complete and accurate translations of the current approved REMS and REMS materials.

Regarding your NDA for Pomalidomide, the REMS you have submitted is adequate to allow our initial review for this application. Upon approval of the harmonized REMS documents, please submit an amended REMS package to match the harmonized product.

If you have any questions, call Theresa Ferrara, Regulatory Project Manager, at (301) 796-2848

Sincerely,

{See appended electronic signature page}

Robert C. Kane, MD
Deputy Director for Safety
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

103 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ROBERT C KANE
10/18/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 204026

PROPRIETARY NAME REQUEST
WITHDRAWN

Celgene Corporation
400 Connell Drive, Suite 7000
Berkeley Heights, NJ 07922

ATTENTION: Paul McInulty
Director, Regulatory Affairs

Dear Mr. McInulty:

Please refer to your New Drug Application (NDA) dated April 10, 2012, received April 10, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for pomalidomide capsules, 1 mg, 2 mg, 3 mg, and 4 mg.

We acknowledge receipt of your September 18, 2012, correspondence, on September 18, 2012, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4) This proposed proprietary name request is considered withdrawn as of September 18, 2012.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Cristina Makela, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-6632. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Amy Baird at (301) 796-4669.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
10/05/2012

From:	Martin, Jewell
To:	"Sigita Zibas"
Subject:	Information Request for NDA 204026
Date:	Wednesday, September 12, 2012 2:45:00 PM

Hello Ms. Zibas,

Please refer to your original NDA application for NDA 204026 Pomalidomide (Capsules), dated April 10, 2012. Please provide your response to this information request by October 30, 2012.

1. The provided dissolution information is incomplete, please submit the following;

- The complete data supporting the selection of the proposed method. Also include your rationale for the selection of this test.
- Include detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. Also include the data for the testing conducted to show the discriminating capability of the selected test.

2. Submit the complete dissolution profile data (raw data, mean values, and SD; n=12 capsules) from the clinically tested batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value).

In addition to formally submitting your responses to your NDA, please send me a courtesy copy via email. Please confirm receipt this email, and do not hesitate to contact me should you have any questions.

Best,

Jewell

Jewell D. Martin, MA, MBA, PMP
Product Quality Regulatory Project Manager

Office of New Drug Quality Assessment
Food and Drug Administration
White Oak Building 21, Rm 2625
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

(301) 796-2072
jewell.martin@fda.hhs.gov

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/s/

JEWELL D MARTIN
09/12/2012

Baird, Amy

From: Baird, Amy
Sent: Friday, August 31, 2012 3:55 PM
To: Christina Kish; 'Paul McInulty'
Subject: NDA 204026 Pomalidomide - FDA Clinical Pharmacology Request

Christina and Paul,

Please refer to the NDA application for NDA 204026 Pomalidomide dated April 10, 2012, which provides for the proposed indication "Pomalidomide in combination with dexamethasone is indicated for patients with relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy."

Per the request of the Clinical Pharmacology review team, provide a response to the following questions. Please provide your response via email NLT September 6, 2012, and follow-up with an official submission to the NDA.

Clinical Pharmacology

As discussed at the pre-NDA meeting and the Sponsor NDA presentation, provide a status update for the following ongoing/planned studies:

-Renal Impairment Study (MM-008)
-Hepatic Impairment Study (CP-XXX)
-In-vivo DDI studies assessing the impact of CYP3A4, 1A2 and P-gp inhibitors/inducers on Pomalidomide exposure
-Thorough QT study

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
08/31/2012

Baird, Amy

From: Baird, Amy
Sent: Friday, August 31, 2012 12:03 PM
To: Christina Kish; Paul McInulty
Subject: NDA 204026 Pomalidomide - FDA Clinical Request

Christina and Paul,

Please refer to the NDA application for NDA 204026 Pomalidomide dated April 10, 2012, which provides for the proposed indication "Pomalidomide in combination with dexamethasone is indicated for patients with relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy."

Per the request of the Clinical review team, provide a response to the following questions. Please provide your response via email NLT COB September 4, 2012, and follow-up with an official submission to the NDA.

Clinical

1. Provide a status update for the expanded access program: number of open sites, number of patients enrolled, total planned number of sites, timeline for opening sites.

2. Provide a status update for the following clinical trials:CC-4047-MM-003, CC-4047-MM-005, and CC-4047-MM-007. Please include number of patients enrolled, planned total number of patients, number of sites (current and planned total) and actual or estimated milestones (study start date, completion of patient accrual, final data collection date for primary endpoint, study completion date).

3. Have there been any pregnancies reported in female patients treated with pomalidomide, or in female partners of male patients treated with pomalidomide? If yes, please include detailed reports regarding the pregnancies. Please also include the data cut-off date in your response.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
08/31/2012

Baird, Amy

From: Baird, Amy
Sent: Monday, August 27, 2012 1:44 PM
To: Christina Kish; Paul McInulty
Subject: NDA 204026 Pomalidomide - Submission dated 8/24/2012

Christina,

Please refer to Celgene's submission dated August 24, 2012, which provides responses to the FDA Microbiology review team's request for information. Please see below.

CELGENE RESPONSE to FDA Question #2:
Microbial limits testing will be performed annually on the validation batches. The post-approval stability protocol will be updated to include annual microbial limits testing for the validation batches. There is no commitment to perform microbial limits testing on annual routine production batches placed on stability.

FDA Request:
It is stated that microbial limits testing will be performed annually and that the post approval stability protocol will be updated to include annual microbial limits testing. However, it is also stated that there is no commitment to perform microbial limits testing on annual routine production batches placed on stability. The reviewers find these statements to be contradictory. Please confirm that microbial limits testing will be performed on one batch of drug product produced annually, whether it is called a validation batch or a stability batch.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
08/27/2012

MEMORANDUM OF MEETING MINUTES

Meeting Type	Teleconference
Time	August 3, 2012; 2:30 – 3:00 PM (EST)
Meeting Location	WO Bldg 22, Rm 4311
Application Number	NDA 204026
Product	pomalidomide capsules, 1 mg, 2 mg, 3 mg, and 4 mg
Indication	relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy
Applicant	Celgene Corporation
Meeting Chair	Kellie Taylor
Meeting Recorder	Sue Kang

FDA Attendees

DMEPA/OSE

Kellie Taylor, Deputy Division Director
Yelena Maslov, Safety Evaluator, Team Leader
Sarah Vee, Safety Evaluator

OSE

Sue Kang, Safety Regulatory Project Manager

Applicant Participants

Celgene Corporation

Michael Faletto, Regulatory Affairs
Paul McInulty, Regulatory Affairs
Christina Kish, Regulatory Affairs
Christopher Griffett, Regulatory Affairs
Chris Linzer, Market Access
Paul Sheehan, Celgene Customer Care Center

Background

Celgene Corporation submitted a Request for Proprietary Name Review on April 12, 2012, received April 12, 2012, to NDA 204026 for [redacted] (b) (4) (pomalidomide) indicated for relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. An alternate name was not proposed by the applicant.

On July 6, 2012, DMEPA denied the proposed proprietary name, [redacted] (b) (4)

2 Pages has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KELLIE A TAYLOR
08/09/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 204026

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Celgene Corporation
400 Connell Drive
Suite 7000,
Berkeley Heights, NJ 07922

ATTENTION: Paul McInulty
Director, Regulatory Affairs

Dear Mr. McInulty:

Please refer to your New Drug Application (NDA) dated April 10, 2012, received April 10, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pomalidomide Capsules, 1 mg, 2 mg, 3 mg, and 4 mg.

We also refer to your April 12, 2012, correspondence, received April 12, 2012, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

(b) (4)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Amy Baird at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204026

FILING COMMUNICATION

Celgene Corporation
Attention: Paul McInulty
Director, Regulatory Affairs
400 Connell Drive, Suite 7000
Berkeley Heights, NJ 07922

Dear Mr. McInulty:

Please refer to your New Drug Application (NDA) dated April 10, 2012, received April 10, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Pomalidomide (Capsules).

We also refer to your amendments dated April 12, May 11 and 31, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is February 10, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 23, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period

copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Acting Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
06/15/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204026

NDA ACKNOWLEDGMENT

Celgene Corporation
Attention: Paul McInulty
Director, Regulatory Affairs
400 Connell Drive, Suite 7000
Berkeley Heights, NJ 07922

Dear Mr. McInulty:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Pomalidomide (Capsules)

Date of Application: April 10, 2012

Date of Receipt: April 10, 2012

Our Reference Number: NDA 204026

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 9, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Amy Baird
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

AMY C BAIRD
06/06/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	May 25, 2012
TIME:	2:10-2:20pm (EST)
LOCATION:	TCON/CDER WO 2560
APPLICATION:	NDA 204026
DRUG NAME:	Pomalidomide
TYPE OF MEETING:	FDA initiated TCON
MEETING CHAIR:	Janice Brown, CMC Team Lead
MEETING RECORDER:	Jewell Martin, Regulatory Health Project Manager
MEETING PURPOSE:	The purpose of the TCON lack of stability data for Celgene Sarl site.

FDA Attendees:
Sarah Pope Miksinski, PhD, CMC Branch Chief
Janice Brown, MS, CMC Lead
Tien Mien Chen,PhD, Biopharm Reviewer
Angelica Dorantes, PhD, Biopharm Team Leader
Jewell Martin, Regulatory Health Project Manager

Celgene Attendees:
Rick Couch, Executive Director, Regulatory CMC
Sigita Zibas, PhD, Associate Director, Regulatory CMC
Anthony Tutino, MS, RPh, Executive Director, Pharmaceutical Development
Anil Menon, Director, Pharmaceutical Development
Paul McInulty, Director, Regulatory Affairs

Meeting Notes:

The Agency told the sponsor that the NDA should come in complete; otherwise the Sarl site information may not be reviewed. Acceptability may be a significant review issue. The stability data may or may not be reviewed depending on where CMC is in review cycle.

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/s/

JEWELL D MARTIN
07/19/2012

JANICE T BROWN
07/19/2012

Baird, Amy

From: Baird, Amy
Sent: Monday, May 14, 2012 5:08 PM
To: Paul McInulty
Subject: NDA 204026 Pomalidomide - DMF Deficiencies

Paul,

Please refer to the NDA application for NDA 204026 Pomalidomide dated April 10, 2012, which provides for the proposed indication "indicated for patients with relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy."

DMF (b) (4) has been found inadequate to support your NDA, and the DMF holder received deficiency correspondences dated May 9, 2012, and May 11, 2012.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
05/14/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	May 3, 2012
TIME:	3:30PM- 3:45PM (EST)
LOCATION:	TCON
APPLICATION:	NDA 204026
DRUG NAME:	Pomalidomide Capsules
TYPE OF MEETING:	FDA initiated TCON
MEETING CHAIR:	Janice Brown, CMC Lead
MEETING RECORDER:	Jewell Martin, Regulatory Health Project Manager

FDA ATTENDEES:
Sarah Pope Miksinski, PhD, CMC Branch Chief
Janice Brown, MS, CMC Lead
Tien-Mien Chen, PhD, Biopharmaceutics Reviewer
William Adams, PhD, CMC Reviewer
Jewell Martin, MA, MBA,PMP, Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:
Celgene Corporation
Rick Couch, Executive Director, Regulatory CMC
Sigita Zibas, PhD, Associate Director, Regulatory CMC
Paul Kurtulik, PhD, VP, Quality and Development
Anthony Tutino, MS, RPh, Executive Director, Pharmaceutical Development
Anil Menon, Director, Pharmaceutical Development
Paul McInulty, Director, Regulatory Affairs

BACKGROUND:

FDA requested a teleconference with Celgene on May 3, 2012 to discuss the following Issues concerning NDA 204026:

1. The submission included 9 months of long term and 6 month accelerated stability data for batched produced at (b) (4) According ICH Q1A (R2), long term testing should cover a minimum of twelve months' duration on at least 3 primary batches at the time of submission; however, the submission included only 9 months stability data. Your submission indicates that the date of manufacture primary stability batches is (b) (4) . Could you submit 12 month data for the primary stability batches before the June 9th filing date?

2. The NDA lists (b) (4) and Celgene Sarl site as drug product manufactures; however, no batch data or comparative accelerated stability data was provided for the Celgene Sarl site. Currently, the agency is assessing the filability of your NDA. Could you confirm that this information was not included in the NDA?

DISCUSSION POINTS:

Celgene Comments for Issue #1:
12 month data was available as of Thursday, May 2, 2012. Information can be made available to FDA by email COB Tuesday, May 8, 2012, and submitted to NDA on Friday, May 11, 2012.

Celgene Comments for Issue #2:
Celgene confirmed that no data was submitted for the Sarl site; however, the process validation campaign starts at the Celgene Sarl site next week. Demonstration work has been done there and there is no difference in the process, formulation, or equipment being used. Celgene does not expect any difference in the quality of the product produced at this facility.

FDA Comments for Issue #2:
In general, FDA requires submission of release data for 3 batches of each strength, plus 3 months of comparative accelerated data. To set the dissolution acceptance criterion, additional comparative dissolution profile data (3 batches of each strength) will be needed as well. Celgene can submit this data before filing date (June 9, 2012) or withdraw the site from the application. Celgene can take time to consider a path forward, but right now we are looking at a site with no data. Most of ONDQA recommendations are completed a week prior to the filing. Please respond back before that timeframe.

Celgene Comments for Issue #2:
(b) (4)

ACTION ITEMS:

Celgene will provide 12 month stability data for batches produced at (b) (4) to FDA by email COB Tuesday, May 8, 2012, and submitted to NDA on Friday, May 11, 2012.

(b) (4)

ATTACHMENTS/HANDOUTS:

None Provided

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/s/

JEWELL D MARTIN
05/21/2012

JANICE T BROWN
05/22/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 066188

MEETING MINUTES

Celgene Corporation
Attention: Paul McInulty
Director, Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

Dear Mr. McInulty:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Pomalidomide (Capsules).

We also refer to the meeting between representatives of your firm and the FDA on September 13, 2011. The purpose of the meeting was a pre-NDA discussion for the indication "treatment of patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies, including lenalidomide and bortezomib."

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Amy Baird, Regulatory Project Manager at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C.
Lead Clinical Analyst
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 13, 2011 12:30pm
Meeting Location: WO 22, Conference Room 1313

Application Number: IND 066188
Product Name: Pomalidomide (Capsules)
Indication: Treatment of patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies, including lenalidomide and bortezomib.
Sponsor/Applicant Name: Celgene Corporation

Meeting Chair: Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C.
Meeting Recorder: Amy Baird

FDA ATTENDEES

Ann T. Farrell, M.D., Acting Director, DHP
Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C., Lead Clinical Analyst, DHP
R. Angelo De Claro, M.D., Clinical Reviewer, DHP
Nicole Gormley, M.D., Clinical Reviewer, DHP
Mark Rothmann, Ph.D., Biometrics Team Leader, DB5
Yun Wang, Staff Fellow, DBV
Joseph Grillo, Ph.D., Clinical Pharmacology Reviewer, DCP5
Janice Brown, Ph.D., Pharmaceutical Assessment Lead, ONDQA
Cynthia Lacivita, Lead Interdisciplinary Scientist, DRISK
Reema Jain, Pharmacist, DRISK
Anwar Goheer, Ph.D., Pharmacology/Toxicology Reviewer, DOP1

SPONSOR ATTENDEES

Kenneth Anderson, M.D., Clinical Advisor, Dana-Farber
Jean-Pierre Bizzari, M.D., Sr Vice Pres., Group Head of Oncology/Hematology
Graham Burton, M.D., Sr. Vice Pres., Regulatory Affairs, Pharmacovigilance & Comp.
Min S. Chen, Ph.D., Principle Biostatistician, Biostatistics
Rick Couch, Sr. Director, Global Regulatory CMC
Robert DeLap, M.D., Ph.D., Vice Pres., Global Medical Research
Michael B. Faletto, Ph.D., Sr. Director, Regulatory Affairs
Christian Jacques, M.D., Vice Pres., Clinical Development
Paul McInulty, Director, Regulatory Affairs
Zhinuan Yu, Ph.D., Director, Biostatistics and SAS Programming
Mohamed Zaki, M.D., Ph.D., Executive Director, Clinical Development
Kamal Shah, Head Global Trials Safety Surveillance
Maria Palisano, Celgene
Julia Hui, Ph.D., Director, Toxicology
Owen Vaughan, Celgene

1.0 BACKGROUND

Pomolidomide (b) (4) is an immunomodulatory agent with a dual mechanism of action consisting of tumoricidal and immunomodulatory effects. The available formulations for clinical development are (b) (4), 1 mg, 2 mg, 3 mg, 4 mg and 5 mg gelatin capsules. The sponsor reports that single-agent pomalidomide demonstrated anti-tumor activity in *in vivo* tumor models of MM and therapy resistant ALL.

2. DISCUSSION

Clinical Questions

Question 1: ***Considering the observed efficacy and acceptable safety profile of pomalidomide in this heavily pretreated MM patients with no available therapies, does the Agency agree that the data for pomalidomide plus dexamethasone in the proposed patient population support the submission of a marketing application for accelerated approval under 21 CFR 314 Subpart H?***

FDA Response to Question 1:

No. The Agency does not agree that clinical trial MM-002 can support filing or review of an application.

Accelerated approval requires demonstration of meaningful therapeutic benefit over available therapy.

MM-002 does not isolate the treatment effect of pomalidomide. Differences in efficacy measures (i.e., PFS, response rate) between treatment arms describe the treatment effect of low-dose dexamethasone.

You did not provide adequate evidence that your proposed population does not have available therapy. Not all patients had received and failed available therapy (e.g., Doxil, cyclophosphamide, melphalan, carmustine, thalidomide). The determination as to whether the available therapy standard has been met is made at the time of NDA action.

Your definition of refractory (documented PD during or within 60 days) remains problematic. MM-002 only requires prior treatment with at least 2 cycles of lenalidomide and at least 2 cycles of bortezomib. Hence, your refractory population would be heterogeneous because it would include patients who receive suboptimal therapy (e.g., patient discontinuing after 2 cycles for reasons other than PD such as patient decision).

Recently published data on retreatment with lenalidomide, thalidomide, and bortezomib, also calls into question the ability to adequately define "failure of therapy".

We remind you of previous advice given on 14 February 2011, "In general, the multiple available therapies in multiple myeloma make it difficult to adequately define a refractory population."

Celgene Response:

Celgene considers that the current clinical and non-clinical data reflects the synergistic activity of pomalidomide plus low-dose dexamethasone providing a meaningful therapeutic benefit over existing treatments. Clinical Study MM-002 demonstrates a response rate of 30.1%, including 6 complete responses (1 confirmed complete response) and a median durability of 32wks. In this patient population the overall survival was 62.6 weeks. These responses are seen in an extremely refractory population as documented by the extent of prior treatment and poor responsiveness to recent treatment. Regardless of exposure or refractoriness to prior treatments the response rate is very consistent.

Celgene does not agree that the population entered into clinical study MM-002 is heterogeneous with respect to sub-optimal therapy. Patients entered into the study must have progressed on the last treatment. Furthermore, patients in MM-002 have received substantially more than the protocol defined minimum of 2 cycles of bortezomib and lenalidomide. The median duration of prior treatment with lenalidomide was 58.4 weeks and prior treatment with bortezomib was 43.1 weeks in the pomalidomide plus dexamethasone arm. Less than 3% of patients progressed within 2 cycles of either lenalidomide and/or bortezomib.

With respect to issues of refractoriness, retreatment, and an accelerated approval population, we would welcome Agency discussion.

FDA Discussion:

The Agency stated that the sponsor could submit trial 002 for accelerated approval, but the Agency could not confirm the appropriateness for filing. The Agency requests that Celgene submit information regarding what agents with regular approval for Multiple Myeloma patients in trial MM-002 had received before enrollment.

Question 2: Celgene plans to conduct the proposed CC-4047-MM-005 (b) (4) ***study (Appendix B) as a well-controlled study confirming clinical benefit in patients with relapsed and refractory multiple myeloma.***

a. Does the Agency agree with Study Protocol CC-4047-MM-005 as designed; the first part to determine the dose to be tested in the second part of the study, where the safety and efficacy of the pomalidomide plus bortezomib plus low-dose (LD) dexamethasone will be assessed?

FDA Response to Question 2a:

The Agency agrees with the Part 1 of clinical trial MM-005. See response to Question 2(d) regarding Part 2.

Celgene Response:

No further discussion is requested for this question.

b. Does the Agency agree that the inclusion/exclusion criteria adequately define the proposed relapsed and refractory multiple myeloma subject population who are refractory to lenalidomide)?

FDA Response to Question 2b:

No. See response to Question 1, regarding problems with the definition of refractory.

Celgene Response:

Celgene anticipates further Agency guidance will be provided with respect to Question 1 above will preclude any need for further discussion of this Question 2b.

c. Does the Agency agree with the choice of bortezomib plus low-dose Dexamethasone as the control arm?

FDA Response to Question 2c:

Yes, we agree with the choice of bortezomib plus low-dose dexamethose in study MM-005. However, you did not provide justification for the estimated (b) (4) median PFS duration for this arm.

Celgene Response:

The justification for the estimated (b) (4) median PFS duration was provided by Multiple Myeloma Key Opinion Leaders. No further discussion is needed for this question.

d. Acknowledging the need for review, does the Agency agree that PFS of an appropriate magnitude is an acceptable primary endpoint for a full approval in the proposed phase 3 study of pomalidomide plus bortezomib plus low-dose dexamethasone vs. bortezomib plus low-dose dexamethasone in relapsed and refractory MM?

FDA Response to Question 2d:

The Agency does not consider a (b) (4) improvement in median PFS to be clinically meaningful.

In general a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for regulatory decision. However, you should be aware that PFS is subject to ascertainment bias and the results of the analysis may be influenced by any imbalance in assessment dates or missing data between treatment arms.

- Progression events should be confirmed by blinded independent review if the study is unblinded or the blinding is unlikely to conceal the therapy.

- Also note that a statistically significant difference in PFS may not necessarily demonstrate a clinically meaningful difference.
- We discourage using interim results of PFS to make a claim of efficacy.
- Overall survival should be considered as a secondary endpoint, or as a co-primary endpoint with alpha allocation.

Celgene Response:

The proposed study is intended to be of sufficient size to allow (b) (4) power for overall survival analysis, which results in over-powering for PFS. Celgene appreciates the additional design comments provided above and does not request further clarification.

e. Does the Agency agree with the proposed secondary endpoints in the proposed (b) (4) part of the study of pomalidomide in relapsed and refractory Multiple Myeloma?

FDA Response to Question 2e:

No. Time to response endpoints are not acceptable.

If the primary endpoint is not achieved, the secondary endpoints would not be reviewed for regulatory action. In the event that there is a statistically significant result for the primary analysis of the primary endpoint, and FDA determines that flaws in the design and/or modifications in the study over time do not confound the reliability and confidence in the results, those secondary endpoints that are significant after proper adjustment for multiplicity may be included in the label. Please include in a future submission, any secondary endpoints for which claims may be included in the labeling and how adjustments will be made for multiplicity to guarantee an overall 1-sided 0.025 study-wise type I error rate.

The Agency recommends an interim analysis for OS at the time of final PFS analysis.

Celgene Response:

No further discussion is requested for this question.

f. Does the Agency agree that the proposed CC-4047-MM-005 study is an acceptable confirmatory story?

Please note that the ongoing global CC-4047-MM-003 Phase 3 study will serve as an additional confirmatory study evaluating and isolating the activity of high-dose dexamethasone alone and confirming activity of pomalidomide with low-dose dexamethasone.

FDA Response to Question 2f:

No. See response to Question 1, 2(b), 2(d), and 2(e).

MM-005 may be able to support an application if deficiencies in 2(b), 2(d), and 2(e) are adequately addressed.

Regarding MM-003, we remind you of FDA advice sent to you on 29 April 2011:

"Study CC-4047-MM-003 is not acceptable for registration because of the following:

a. The study design (high-dose dexamethasone alone vs. pomalidomide + low-dose dexamethasone) does not isolate the effect of pomalidomide. In addition, we reiterate our concern on the relevance of high-dose dexamethasone to the US patient population as several chemotherapy regimens for multiple myeloma have already shown benefit over high-dose dexamethasone.

b. We disagree with your definition of a refractory and relapsed multiple myeloma population. As discussed during our February 14, 2011 meeting, you should provide justification for why other therapies that could be considered available therapy would not have produced meaningful responses in this patient population."

Celgene Response:

We acknowledge your comments on Clinical Study MM-005. Upon agreement that a submission can be made based on Clinical Study MM-002, clinical study MM-005 would be the confirmatory study.

Clinical Data Presentation Questions

Question 3: ***Per the guidance on the FDA website, "Study Data Standards for Submission to CDER", Celgene would like to discuss the following proposal with the review division on dataset presentation in the NDA:***

- ***Datasets from the two company sponsored clinical studies conducted in the proposed indication, CDC-407-00-001/CC-4047-MM-001 (titled "An Open-Label Study of the Safety and Efficacy of CC-4047 Treatment for Patients with Relapsed Multiple Myeloma") and CC-4047-MM-002, will be converted to SDTM format, following SDTM v1.2 and SDTM IG v3.1.2, and both SDTM and ADaM datasets will be included in the NDA for both studies. The Clinical Study Report for CC-4047-MM-001 contains only clinical pharmacokinetic and safety data.***

- ***For supportive clinical studies not in the proposed indication and non- Celgene sponsored studies, raw clinical databases and derived analysis datasets will be provided in the structure used for the analysis of each individual study. For these studies, Celgene does not plan to perform further post-processing to CDISC SDTM format.***

Does the Agency agree with the above proposal?

FDA Response to Question 3:

We do not recommend you submit an application based on MM-002 and/or MM-003. See response to Question 1.

In general, your proposal for submitting supportive study datasets is acceptable; consider the following:

- Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.

- Provide all concentration-time and derived PK parameter datasets for all studies. In the study reports, present the PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.

For any population PK models all datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results. Please refer to the following pharmacometric data and models submission guidelines (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm).

The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the NDA submission.

Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will be appearing in the label.

For efficacy and safety analysis datasets, you are encouraged to follow the practice noted in the Study Data Specifications, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf).

To facilitate the review process, efficacy information including patient disposition, demographics, and derived primary and secondary endpoints should be included in one analysis dataset for each study unless the data structures are not compatible due to the nature of the endpoints, e.g., one record per patient type of endpoint vs. multiple records per patient type of endpoint.

Celgene Response:

No further discussion is requested for this question.

Question 4: Efficacy data for the proposed NDA will be provided by a Celgene sponsored study and a study performed by the (b) (4) ***In lieu of an integrated summary of efficacy data (ISE), Celgene proposes to provide only a Clinical Summary of Efficacy in Module 2. Is this acceptable to the Agency?"***

FDA Response to Question 4:

No. We do not agree with your planned submission. See response to Question 1.

Celgene Response:

If the Agency finds our response under Q1 acceptable in support of a submission of the proposed NDA, can the Agency provide a response to Question 4?

Safety Data Presentation Questions

Question 5: Does the Agency agree with Celgene's plan to provide individual patient safety narratives?

FDA Response to Question 5:

Yes. However, we do not agree with your planned submission. See also response to Question 1.

Celgene Response:

Celgene acknowledges and appreciates the Agency's comments. No further discussion is needed for this question.

Question 6: The Sponsor proposes that the full Integrated Summary of Safety (ISS) will be placed in Module 5 (section 5.3.5.3), with the text portion repeated in section 2.7.4 since it will be sufficiently detailed to serve as the Clinical Summary of Safety, and will be concise enough to meet the suggested size limitations for Module 2 (section 2.7.4). Is this acceptable to the Agency? Does the Agency have any comments on the outline of the

Clinical Summary?

FDA Response to Question 6:

We do not agree with your planned submission. See response to Question 1.

Celgene Response:

If the Agency finds our response under Q1 acceptable in support of a submission of the proposed NDA, can the Agency provide a response to Question 4?

CMC Questions

Question 7: The proposed NDA stability package will include 6 months real time (b) (4) ***and 6 months accelerated data*** (b) (4) ***for the proposed four commercial strengths (1, 2, 3 and 4 mg) at the time of submission. The submission will also be supported by real time data of up to 36 months for the 1, 2 and 3 mg strengths. The 1 mg and 2 mg capsules are filled*** (b) (4) ***and the 3 mg and 4 mg are filled*** (b) (4) ***. Both blends*** (b) (4) ***. The capsule shells used for registration stability represent*** (b) (4) ***The stability data presented in this briefing document (Section 6.1.3.5), along with 12 month registration stability data provided during the review period, will be used to justify a shelf life of*** (b) (4) ***Is the proposed stability data package with the available dye combination acceptable to the Agency?***

FDA Response to Question 7:

Include in your NDA at least 12 months long term stability and 6 months of accelerated stability for the 4 mg strength in the NDA since there is no supportive stability data for the 4 mg strength in the registration batches. Your proposal to include 6 months of long term and accelerated stability data for the 1 mg, 2 mg and 3 mg strengths using the commercial capsule shells is reasonable, provided that the supportive data are acceptable and are adequately indicative of overall quality. A determination of the shelf life will be a review issue.

Celgene Response:

Celgene has used pomalidomide (b) (4) ***capsules in early clinical trials.*** (b) (4) ***Therefore, there is stability data that brackets the 4 mg capsule. Based on the*** (b) (4) ***supportive stability data, would it be acceptable to file with 6 months (real time and accelerated) stability data on the 4 mg capsule? Celgene will provide the*** (b) (4) ***stability data as well as the composition of the*** (b) (4) ***capsule in the NDA submission. Also, Celgene will provide***

updated stability data throughout the NDA review process as it becomes available.

FDA Discussion:

It is difficult to give a definitive response due to the limited information provided for the (b) (4) (b) (4) strength. We recommend you submit a summary of the comparisons to bracket the 3 and (b) (4) strengths.

Non-Clinical Question

Question 8: ***An overview of the non-clinical data is provided in Section 6.2 of this briefing document. In addition, a draft table of contents for Module 4, listing all non-clinical studies to support the NDA is included in Appendix C. Based on the overview of the non-clinical data, does the Agency agree that the non-clinical package is adequate to support a submission?***

FDA Response to Question 8:

Your completed nonclinical toxicology studies appear adequate to support NDA filing; however, final determination of the acceptability of the study results is a review issue which can only be determined following reviews of full study reports.

Celgene Response:

Celgene acknowledges the Agency's comment and will provide the full study reports in the NDA. No further discussion is needed for this question.

Regulatory Questions

Question 9: ***The Sponsor will submit the NDA in electronic format using the electronic common technical document (eCTD) specifications as described in the FDA Guidance for Industry, "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" (June 2008, Electronic Submissions, Revision 2). In this eCTD submission, the individual document format will follow the CTD guideline. Is this acceptable to the Agency?***

FDA Response to Question 9:

We do not agree with your planned submission. See response to Question 1.

Celgene Response:

If the Agency finds our response under Q1 acceptable in support of a submission of the proposed NDA, can the Agency provide a response to Question 4?

Question 10: ***A listing of documents/data to be submitted in this NDA according to Module number is provided in Appendix C. Does the Agency agree to the overall list of documents/data for this NDA as presented in Appendix C?***

FDA Response to Question 10:

We do not agree with your planned submission. See response to Question 1.

Celgene Response:

If the Agency finds our response under Q1 acceptable in support of a submission of the proposed NDA, can the Agency provide a response to Question 4?

Question 11: ***Does the Agency have any further comments regarding the approach to the format and content of the NDA submission, as outlined in the above questions?***

FDA Response to Question 11:

See clinical pharmacology comments below.

Celgene Response:

Celgene acknowledges and appreciates the Agency's comments. Please see our response to the clinical pharmacology comments below.

REMS Questions

Question 12: ***Assuming that FDA may require new IMiD products such as pomalidomide have REMS with ETASU tied to drug distribution for marketing (similar to S.T.E.P.S. and RevAssist REMS), is the REMS proposal outlined in Section 6.4 and the proposed REMS provided in Appendix E acceptable to the Agency?***

FDA Response to Question 12:

The Agency considers it premature to address this issue at this time.

The proposed REMS submitted is consistent with the current approved REMS for Revlimid. We acknowledge the upcoming meeting with Celgene on September 27, 2011 to discuss harmonization of STEPS and RevAssist. Assuming FDA requires a similar REMS, we agree a more uniform approach for healthcare providers and patients to increase efficiency and reduce burden across this class of products should be implemented.

We remind you that a complete review of the proposed REMS, including all proposed REMS education and communication materials in conjunction with the full clinical review after the NDA is submitted will be necessary to determine whether the proposed REMS is acceptable, since additional information regarding risks and safe product use may emerge during the

review of the NDA.

Celgene Response:

Celgene acknowledges and appreciates the Agency's comments. No further discussion is needed for this question.

Question 13: Consistent with RevAssist and S.T.E.P.S., Celgene plans to propose a tradename for the REMS program for pomalidomide, to be included in the REMS documents submitted in the NDA. How soon should Celgene anticipate receipt of FDA feedback regarding acceptability of this tradename?

FDA Response to Question 13:

See response to Question 12.

Celgene Response:

Celgene acknowledges and appreciates the Agency's comments. No further discussion is needed for this question.

3.0 Additional FDA Comments

1. Regarding the PK/Population PK study design in Phase 3 Trial, we have following comments:
    - In addition to the proposed sparse PK sample scheme in Part 2, you should collect steady state trough concentrations to obtain a precise estimate of CL/F in the patient population. These data can be pooled with data from Part 1 and analyzed using Population PK approach to assess the effects of covariates (e.g., demographics and organ dysfunction) on pharmacokinetic parameters.

    - You should enroll patients with varying degrees of renal (mild to moderate) and hepatic impairment in your PK substudy to assess the effect of organ dysfunction in the population PK model.

    - Perform exposure-response analysis of the Phase 3 data to link the exposure (i.e., observed or model predicted) to efficacy and safety endpoints. You ought to collect steady state trough concentrations in as many patients as possible in order to conduct meaningful exposure-response analyses.

    Celgene Response:

    Celgene acknowledges and appreciates the Agency's comments. No further discussion is needed for this question.

2. Based on our review of the submitted supportive information and the proposed NDA content and structure we note the following issues appear to be omitted and will likely be

review issues. Many of these were communicated to you at your 03/25/2010 EOP2 meeting.

- Based on the reported results of your mass balance study in humans it appears that pomalidomide is extensively metabolized in the liver. Given this finding you should assess the affect of hepatic impairment on the exposure of pomalidomide and any active metabolites. Please refer to the FDA Guidance at

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf

- Based on the reported results of your mass balance study in humans it appears that pomalidomide is extensively eliminated in the urine. Given this finding, you should assess the affect of renal impairment on the exposure of pomalidomide and any active metabolites. Please refer to the FDA Guidance at

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072127.pdf

- In your supporting information section you state that CYP1A2 and CYP3A4 are the primary human P450 enzymes responsible for the in vitro hydroxylation of pomalidomide; however, you do not assess the affect of inhibitors of these enzymes on the exposure of pomalidomide and any active metabolites in humans. In your application you should provide substantial evidence why this was not assessed or evaluate this issue in humans. Please refer to the FDA Guidance at

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072101.pdf

- In your supporting information section you state that Pomalidomide is a substrate of P-glycoprotein in vitro; however, you do not assess the affect of inhibitors of this transporter on the exposure of pomalidomide and any active metabolites in humans. In your application you should provide substantial evidence why this was not assessed or evaluate this issue in humans. Please refer to the FDA Guidance at

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072101.pdf

Celgene Response:

Celgene acknowledges and appreciates the Agency's comments. No further discussion is needed for this question.

3. In the appropriate clinical pharmacology sections of the eCTD include the following:

   - An evaluation of the effects of covariates such as age, weight, gender, race, etc. on the PK (pharmacokinetics) of pomalidomide and any active metabolites.

- Provide a table listing of patients with renal or hepatic impairment who have received pomalidomide, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.

Celgene Response:

Celgene acknowledges and appreciates the Agency's comments. No further discussion is needed for this question.

4. We request that you include the attached Question Based Assessment (see appendix) in addition to the other components of your clinical pharmacology summary that is generally found in Module 2 of the eCTD.

Celgene Response:

Celgene acknowledges the Agency's request and will provide the Question Based Assessment in Module 2 of the eCTD. No further discussion is needed for this question.

4.0 ATTACHMENTS AND HANDOUTS

Question Based Assessment

Appendix

CLINICAL PHARMACOLOGY SUMMARY

1. Goal

In addition to summarizing the relevant findings the goal of the Clinical Pharmacology Summary is to focus sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions a generic questionnaire is provided that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies*)* and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple dose, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 GENERAL CLINICAL PHARMACOLOGY

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t1/2 and AUC.

2.4 Exposure-Response

2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship. Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-effectiveness relationship. Provide point estimate as well as a measure of the inter-subject variability for continuous and categorical endpoints. Indicate proportion of responders, if applicable.

Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, Cmax or Cmin is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Of major interest are safety endpoints determining the therapeutic range. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, Cmax or

Cmin is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) Cmax and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [Cmax, tmax, AUC, Cmax,ss, Cmin,ss, Cmax,ss/Cmin,ss, tmax,ss, AUC0-τ, CL/F, V/F and t1/2 (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, Cmax, Cmin, CL/F and t1/2 of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute bioavailability of drug of parent drug and relative bioavailability, lag time, tmax, tmax,ss, Cmax, Cmax,ss and extent of systemic absorption of parent drug and relevant

metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Provide identification for ≥ 90% of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivities are too small to be assignable to specific metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance (mL/min) in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

2.5.11 What are the characteristics of drug excretion in urine?

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) Cmax and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.13 How do the PK parameters change with time following chronic dosing?

Indicate whether the mean ratio of AUC0-τ at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.5.14 Is there evidence for a circadian rhythm of the PK?

Indicate whether Cmax and Cmin of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, Cmax, clearance, volume of distribution and t1/2 for pairs studied: elderly vs.young, male vs.female, normal body weight vs. obese, race/ethnicity x vs. race/ethnicity y, mild vs. severe target disease

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (dose or interval) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Body Weight

2.6.2.3 Elderly

2.6.2.4 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.5 Race/Ethnicity

2.6.2.6 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC and Cmax of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, Cmax and CL/F on Clcr for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.7 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC and Cmax of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of Cmax, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.8 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of

patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity (NOT applicable to small molecule drugs)

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?

Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Summarize the results of the in vitro studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

2.7.2 Is the drug a substrate of CYP enzymes?

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to Km, controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the in vitro findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for Ki, IC_{50} and Vmax for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as

inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the [I]/Ki ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

2.7.5 Are there other metabolic/transporter pathways that may be important?

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.7 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report the 90% confidence intervals about the geometric mean ratio for AUC and Cmax for the drug of interest in the presence and absence of each of the co-administered drugs. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report 90% confidence intervals about the geometric mean ratio for AUC and Cmax of each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.8 Does the label specify co-administration of another drug?

2.7.9 What other co-medications are likely to be administered to the target population?

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and Cmax after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?

2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to-be-marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

2.9.3 For all moieties measured, is free, bound, or total measured?

Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.5.1 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.5.3 What is the sample stability under conditions used in the study?

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at ≤ –20° C.

2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VIRGINIA E KWITKOWSKI
09/26/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 066188

MEETING MINUTES

Celgene Corporation
Attention: Paul McInulty
Director, Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

Dear Mr. McInulty:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Pomalidomide (Capsules).

We also refer to the meeting between representatives of your firm and the FDA on February 15, 2011. The purpose of the meeting was to obtain feedback from the Agency on the design for a proposed Phase 3 study is support of a full approval for the proposed indication.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Amy Baird
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: IND

Meeting Date and Time: February 15, 2011; 1:00PM – 2:00PM
Meeting Location: White Oak Campus, Building 22

Application Number: IND 066188
Product Name: Pomalidomide (Capsules)
Indication: For the treatment of Multiple Myeloma (MM), (b) (4)

Sponsor/Applicant Name: Celgene Corporation

Meeting Chair: Ann Farrell, M.D
Meeting Recorder: Lara Akinsanya, M.S.

FDA ATTENDEES

Office of the Center Director (OD)

Robert Temple, M.D., Deputy Center Director for Clinical Science

Office of Oncology Drug Products (OODP)

Anthony J. Murgo, M.D., Associate Office Director

Division of Hematology Products (DHP)

Ann Farrell, M.D., Acting Division Director
Edvardas Kaminskas, M.D., Acting Deputy Director
Angelo de Claro, M.D., Ph.D., Medical Officer
Lara Akinsanya, M.S., Regulatory Health Project Manager
Ebla Ali Ibrahim, M.S., Regulatory Health Project Manager
Karen Bengtson, Regulatory Health Project Manager

Division of Drug Oncology Products (DDOP)

Yang-Min (Max) Ning, M.D., Medical Officer

Office of Clinical Pharmacology (OCP)

Julie Bullock, PharmD, Clinical Pharmacology Team Leader
Joseph A. Grillo, Pharm.D., Clinical Pharmacology Reviewer
Anshu Marathe, Ph.D., Pharmacometrics Reviewer
Matt Wolf, Pharmacy Student

Office of Biostatistics, Division of Biometrics V (DBV)

Mark Rothmann, Ph.D., Statistical Team Leader
Hong (Laura) Lu, PhD, Statistician

SPONSOR ATTENDEES

Kenneth Anderson, M.D., Clinical Advisor
Jean-Pierre Bizzari, M.D., Senior VP, Group Head of Oncology/Hematology
Graham Burton, M.D., Senior VP, Regulatory Affairs
Robert DeLap, M.D., Ph.D., Vice President, Global Medical Research
Christian Jacques, M.D., Vice President, Clinical Development
Mohamed Zaki, M.D., Ph.D., Executive Director, Clinical Development
Lisa Wisniewski, Ph.D., Executive Director, Global Project Leader
Zhinuan Yu, Ph.D., Director, Biostatistics and SAS programming
Xin Yu, Ph.D., Principal Statistician
Michael B. Faletto, Ph.D., Senior Director, Regulatory Affairs
Paul McInulty, Director, Regulatory Affairs

1.0 BACKGROUND

Celgene Corporation requested a type B IND meeting with FDA on October 14, 2010, to obtain feedback from the Agency on the design for a proposed Phase 3 study in support of a full approval for the proposed indication. On October 25, 2010, FDA sent Celgene Corporation the meeting request granted letter.

On February 14, 2011, FDA emailed Celgene Corporation preliminary responses to the questions contained in the meeting information package dated January 12, 2011.

2. DISCUSSION

2.1. Unmet Medical Need Population For Possible Consideration of a Submission For Accelerated Approval

Question 1:

What prior MM treatments would patients need to have received in order to represent an unmet need population with no alternative effective therapies available, including:

- *Number of prior lines of therapy*
- *Specific prior therapies*

FDA Response to Question 1:

The presentation is not clear as to which data are intended to support accelerated approval. Please specify clinical studies you intend to use to support the proposed accelerated approval.

We note that at the February 8, 2011 ODAC meeting, the Committee recommended that the Office of Oncology Drug Products only accept single-arm trial data for accelerated approval in two situations: rare populations (less than 1000 patients) and for agents with high response rates. ODAC also recommended that during negotiations with sponsors regarding confirmatory studies for accelerated approval the Agency should insist that at least two randomized controlled trials be ongoing at the time of the NDA submission.

Discussion:

The Agency and the sponsor have agreed to meet in the future, when the data is fully mature, to discuss the possibility of an accelerated approval based on MM-002 study.

Question 2:

What level of response rate and duration of response does the Agency consider clinically meaningful in such a population?

FDA Response to Question 2:

See FDA response to question 1.

Discussion:

No discussion occurred.

2.2. Proposes Phase 3 Study – CC-4047-MM-003

Question 3:

Celgene submitted a proposed phase 3 study, Study CC-4047-MM-003, titled "A Phase 3, Multicenter, Randomized, (b) (4) *Study to Determine the Efficacy and Safety of Pomalidomide in Combination with Low-Dose Dexamethasone Versus Placebo Plus Low-Dose Dexamethasone in Subjects with Refractory Multiple Myeloma or Relapsed and Refractory Multiple Myeloma" to IND 066188 for Special Protocol Assessment on 1 July 2010 (SN0252), to which the Agency responded on 16 August 2010. Following FDA feedback on the proposed study protocol for Study CC-4047-MM-003, the Sponsor would like to discuss plans for the Phase 3 program for pomalidomide and obtain feedback on its acceptability to support approval in the U.S.*

Please find below the Celgene Responses to the Agency's comments on Special Protocol Assessment. Do the responses provided adequately address the Agency's previous concerns and would the study as proposed support an application for the proposed indication?

Celgene's Question #1 in SPA:

Does the Agency agree that the inclusion/exclusion criteria describe a well-defined refractory or relapsed and refractory Multiple Myeloma subject population who would be expected to have limited or no benefit from further treatment with lenalidomide or bortezomib?

Agency's Response (16 August 2010):

If you define refractory as refractory to lenalidomide and bortezomib, the patient population appears acceptable for the proposed study.

We do not agree that you have defined a population with an unmet medical need for a population that does not have other available therapy.

We recommend that you exclude patients who may be eligible for or plan to have cell transplantation before enrollment.

In addition, reasons for patient's intolerance to lenalidomide or bortezomib after a minimum of 2 cycles of treatment have to be defined in the protocol and documented clearly in the eligibility checklist and CRFs.

Celgene's Response:

Celgene intends to define a patient population (and subsequently a suitable comparator) that is relapsed/refractory to both lenalidomide and bortezomib, not to define an unmet medical need. Based upon the Agency's comments, Celgene has made the following changes to the study design to further clarify and define a patient population.

- Patients who are being considered for or are eligible for stem cell transplantation are now excluded from the study.

(b) (4)

[redacted]

FDA Response to Question 3:

a. We disagree with your definition of a "relapsed and refractory" patient population. Patients relapsing within 60 days of completing therapy may respond to other available therapies.

In general, the multiple available therapies in multiple myeloma make it difficult to adequately define a refractory population.

Celgene's Question #2 in SPA:

Does the Agency agree with the choice of low dose dexamethasone as the control arm?

Agency's Response (16 August 2010):

No. We are concerned that the use of single agent low dose dexamethasone as used in your trial does not reflect US clinical practice particularly for a patient population that is eligible to receive a stem cell transplant and may only have received 2 prior lines of anti-myeloma therapy.

Please provide additional justification that the low-dose dexamethasone arm is not inferior to any other regimen patients in your study are eligible to receive.

Celgene's Response:

The comparator of this study that investigates a population that is refractory to both lenaldiomide and bortezomib has been changed to high-dose dexamethasone. Dexamethasone will now be given at a dose of 40 mg on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle. In the previous version of the protocol, dexamethasone would have been given at a dose of [redacted] (b) (4)

The basis of this change is due to the fact that high-dose dexamethasone continues to be a frequently used therapy in relapsed and/or refractory multiple myeloma in the absence of an alternative of established value for the patient (Richardson, 2005). Of note, high-dose dexamethasone was the comparator in the pivotal studies that led to the approval of THALOMID, VELCADE, REVLIMID (US PI for all), and although use may have declined, it still has a role in the management of myeloma subjects especially those with cytopenias and renal impairment. Furthermore, dexamethasone is included in the NCCN guidelines as an approved therapeutic choice in the salvage setting. Dexamethasone pulses may induce response rates in patients with relapsed myeloma, although the risk of side effects is higher at these doses and responses may be limited in duration. A detailed dose reduction/dose delay schedule has been incorporated into the protocol to accommodate for possible side effects. Because dexamethasone is not cytotoxic, it still has a role in the management of myeloma subjects especially those with cytopenias and renal impairment.

Given the extensive prior treatment commonly received by patients who have been able to be enrolled in recent relapsed/refractory myeloma studies (including the MM-002 study), Celgene has not identified a suitable alternative "standard" therapy or therapies that could be practically used (in place of dexamethasone) across a multicenter randomized study.

Discussion:

The sponsor will provide a justification for why other therapies that could be considered available therapy would not have produced meaningful responses in this patient population.

b. Defining the optimal dexamethasone dose for randomized control trials likely awaits additional randomized comparator trials since the trial comparing Revlimid + low-dose dexamethasone with Revlimid + high-dose dexamethasone was terminated early due to inferior survival in the high dose dexamethasone treatment group.

Several chemotherapy regimens for multiple myeloma have already shown benefit over high dose dexamethasone. The proposed study may have no relevance to the US patient population.

Perhaps Celgene should conduct randomized comparative trials to determine the optimal comparator arm such as Revlimid or Velcade.

Celgene's Question #3 in SPA:

While the sponsor understands that approval would be a review issue, does the Agency agree that PFS is an acceptable primary endpoint for a full approval in the proposed double-blind phase 3 study of pomalidomide plus low dose dexamethasone vs. placebo plus low-dose dexamethasone in refractory or relapsed and refractory MM?

Agency's Response (16 August 2010):

Yes, PFS could be acceptable for an approval decision.

We do not agree that based on the toxicity profile of pomalidomide, it is likely you will be able to blind the study.

Celgene's Response:

This study will no longer use a placebo. As noted above, the study design has been modified to specify the use of high dose dexamethasone alone in the control arm. As a direct result of the differing dose schedules of the dexamethasone in treatment arm versus the control arm, the study will be open-label.

Treatment Arm A consists of pomalidomide plus low-dose dexamethasone, in which a 40 mg dose of dexamethasone (patients ≤ 75 years of age) or 20 mg dose (patients > 75 years of age) is given only on Days 1, 8, 15 and 22 of a 28-day cycle. The pulsed high-dose dexamethasone, the comparator, will be administered on Days 1 through (b) (4) of a 28-day cycle. The starting dose for high-dose dexamethasone is the same as low-dose dexamethasone: 40 mg dose of dexamethasone (patients ≤ 75 years of age) or 20 mg dose (patients > 75 years of age). The protocol is designed to maximize uniformity of timing of assessmens for response / progression, and objectivity of response / progression assessments.

Discussion:

No discussion occurred.

c. Please see FDA response to Question 3b.

Celgene's Question #9 in SPA:

Is the statistical analysis plan section 4.6 (Appendix F) as specified in the protocol acceptable to support registration?

Agency's Response (16 August 2010):

No. An appropriate primary analysis plan should have a one-sided type I error rate at most 0.025 when ignoring the futility boundaries.

In the SAP, Table 2 (Censoring Rules for PFS) lists several scenarios for censoring progression documented between scheduled assessments to the date of events such as for an increase in M-protein, an increase in bone marrow plasmacytosis and plasma cells, development of hypercalcemia (>11.5 mg/dl), or appearance of new soft tissue plasmacytomas or increase in size of existing plasmacytoma(s), or appearance of new lytic bone lesions or increase in size of existing bone lesions. We recommend that you change the date of these events to the date of last adequate assessment with no progression.

Celgene's Response:

The protocol proposes performing the primary analysis for PFS after (b) (4) subjects progress or die during the study (PFS events), (b) (4) for PFS between the two treatment arms at the 2-sided significance level of (b) (4) which is equivalent to a 1-sided alpha of (b) (4)

For the statistical analysis of the primary endpoint (PFS), PDs documented between scheduled assessments will use the dates of last scheduled adequate assessments with no progression as the event dates. Section 10.6.1 of the amended protocol now includes the following description:

All subjects will be followed for PFS until a PFS event has occurred (progression or death) or until the data cutoff. Subjects who withdrew for any reason or received another anti-myeloma therapy without documented PD (as determined by the independent adjudication review committee [IRAC]) will be censored on the date of their last adequate response assessment, prior to receiving any other anti-myeloma therapy. Subjects who are still active at the time of the data cut-off date without PD (as determined by the IRAC) will be censored on the date of their last adequate response assessment. PDs documented between scheduled assessments will use the dates of last scheduled adequate assessments with no progression as the event dates.

Discussion:

No discussion occurred.

d. On Table 11 of your protocol for Study CC-4047-MM-003, the Type I error rate of the final PFS efficacy analysis was adjusted by the alpha level spent at the futility analysis at (b) (4) of event number. An appropriate primary analysis plan should have a one-sided Type I error rate at most 0.025, when ignoring futility boundaries. Therefore, the bound for test statistic for the final efficacy analysis of PFS should be 1.96 instead of (b) (4)

We recommend that patients who withdraw for any reason or receive another anti-myeloma therapy will be continued to be followed for PFS events.

Celgene's Question #11 in SPA:

Does the Agency have any additional comments or suggestions on the study design?

Agency's Response (16 August 2010):

We are concerned about possible unblinding secondary to CC-4047's toxicity in the study.

Protocol violation is listed as a criterion for discontinuation from the study. You should provide more detailed information on the use of this criterion in your protocol.

For each patient who discontinues due to the list on page 63 of your protocol, please provide detailed information on the CRF.

All patients enrolled in the study should be included in the statistical analysis for the primary endpoint. Patients who are discontinued from treatment or the study should be censored at the last complete assessment for PFS.

We recommend the concomitant medications section state that drugs known to prolong the QTc interval be avoided unless deemed medically necessary. Please also provide a comprehensive list of these drugs as an appendix.

Celgene's Response:

As noted above, this study will no longer use a placebo and this is now an open-label study.

The protocol has been amended to remove "protocol violations" as a reason for discontinuation from the study, as reflected below:

Information will be collected on the CRF for patients who discontinue for reasons other than a progression event.

All patients enrolled and randomized (ITT population) will be included in the statistical analysis for all efficacy endpoints. Patients who are discontinued from treatment without an event will continue to be followed for PFS assessment until disease progression. Patients who are discontinued from the study without a PFS event will be censored at the last complete assessment for PFS.

A list of drugs known to cause QTc prolongation is now added as an appendix to Protocol Amendment #1.

Discussion:

No discussion occurred.

e. The response to question #11 regarding restricting concomitant use of drugs that prolong the QTc is acceptable from a clinical pharmacology perspective.

Agency's Additional Comment #4 (16 August 2010):

The protocol should state what specific algorithm (e.g., randomly permuted blocks within strata or dynamic allocation) will be used for generating the random treatment assignments (block size should not be identified in the protocol).

Celgene's Response:

Protocol Amendment #1 now specifies that subjects in this study will be randomized 2:1, using the method of randomly permuted block within strata.

Discussion:

No discussion occurred.

f. Response acknowledged.

Agency's Additional Comment #5 (16 August 2010):

We recommend using a stratified log-rank test [redacted] (b) (4) *for the primary endpoint.*

Celgene's Response:

The primary analysis for PFS has changed from [redacted] (b) (4) to stratified log rank test in Amendment #1.

Discussion:

No discussion occurred.

g. Response acknowledged.

> **Additional significant changes included in the protocol amendment (Protocol Amendment #1, dated 15 October 2010) are also summarized below:**
>
> **Companion Study:** A companion study, Study CC-4047-MM-003/C, titled "*Open-Label, Multi-center, Single-Arm Study for the Safety and Efficacy of Pomalidomide (CC-4047) Monotherapy for Subjects with Refractory or Relapsed and Refractory Multiple Myeloma*" will be available at the same time as the main study protocol Study CC-4047-MM003. Study CC-4047-MM-003/C will enroll subjects who have discontinued from the dexamethasone alone treatment arm (Treatment Arm B) of the main study CC-4047-MM-003 trial due to disease progression. The synopsis of the companion study is attached in Appendix B. Patients may not enter the companion study unless/until disease progression is documented (confirmed by review by an adjudication committee) following at least 2 cycles of treatment with high dose dexamethasone.
>
> **Progression-Free Survival (PFS):** Based on the results from other studies of relapsed refractory MM patients (e.g., CC-5013-MM-009/010 – studies comparing the efficacy and safety of oral lenalidomide in combination with oral pulse high-dose dexamethasone with that of placebo and oral pulse high-dose dexamethasone as treatment for subjects with relapsed or refractory multiple myeloma), the median PFS in patients treated with high-dose dexamethasone alone was about (b) (4) (b) (4) Therefore, the statistical modeling has been revised to incorporate a PFS of (b) (4) for the control arm for CC-4047-MM-003, which has been used in the sample size estimation.

Discussion:

No discussion occurred.

h. Please see FDA responses to 3a and 3b.

Discussion:

No discussion occurred.

FDA Additional Comments:

1. **FDA does not agree that you will be able to meet your exploratory objective of exploring the pomalidomide drug exposure and response relationship by collecting PK data from (b) (4) patients in study CC-4047-MM-003. We recommend that you collect sparse PK sampling in all subjects to evaluate exposure-response relationship for efficacy (i.e., PFS) and safety endpoints.**

   Discussion:

   No discussion occurred.

2. **In the revised protocol for Study CC-4047-MM-003, you proposed to use (b) (4) for the interim and final analyses of OS. However, on Table 11 of**

the protocol, the alpha sharing for the OS analyses used a (b) (4) **between the interim and final analyses. Please clarify.**

Discussion:

No discussion occurred.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

None

5.0 ATTACHMENTS AND HANDOUTS

- Celgene's POM slide presentation discussed at the meeting.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY C BAIRD
03/15/2011